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CLINICAL EVALUATION OF THE BALLISTOCARDIOGRAM

I. NORMAL SUBJECTS

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BALLISTOCARDIOGRAPHY still is an unexplored subject to the modern clinician, despite the fact that this study of the body movements induced by the cyclic motion of the heart and blood was introduced as early as 1877 by Gordon.[1] Following the work of Henderson,[2] in 1905, interest in this new field of investigation lagged until 1939, when Starr[3] presented the first suitable apparatus, a high-frequency, undamped ballistocardiograph. In order to overcome the shortcomings of the Starr machine, Nickerson,[4] in 1944, introduced a low-frequency ballistocardiography table, which could be critically damped for each patient. The long time which elapsed between the introduction of the method of ballistocardiography and its clinical acceptance and application can be accounted for, in large measure, by the unwieldy bulk, the fixed installation, and the costly construction of both the Starr and Nickerson tables.

The present widely renewed interest in ballistocardiography stems principally from the tremendous impetus delivered by the work of Dock and Taubman[5] with their simple apparatus. The patient lies supine upon a sturdy fixed table, and the ballistocardiogram is recorded directly from the body. This is achieved simply by a crossbar across the shins, which imparts motion to the hinge of the Dock recording device. The latter is either a photocell pickup (displacement ballistocardiogram) or a wire coil in a magnetic field (velocity ballistocardiogram). The third piezoelectric method utilizes the special electrical properties of glennite crystals.[6]

The purpose of this investigation was to study the clinical application of this simple method of ballistocardiography and to evaluate the results in a series of normal control subjects.

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METHOD

In the present study of the clinical value of the ballistocardiogram, the photocell displacement type of apparatus, as described by Dock and Taubman,[5] was employed. The patients were placed horizontally upon a rigid, immobile, wooden table, and the records were obtained by placing a crossbar across the shins. The cyclic longitudinal oscillations of the body were then recorded with this device by direct connection to a bipolar lead of an electrocardiographic machine. We used either a Sanborn single or a Sanborn four-channel direct writing Viso-cardiette. The Dock apparatus was modified, in that the hinge was removed, and the crossbar was placed free in the space between the light source and the photocell (Fig. 1). By so doing, we eliminated any element of error due to the various possible placements of the crossbar against the hinge. Records were taken during quiet respiration and on deep inspiration and expiration.

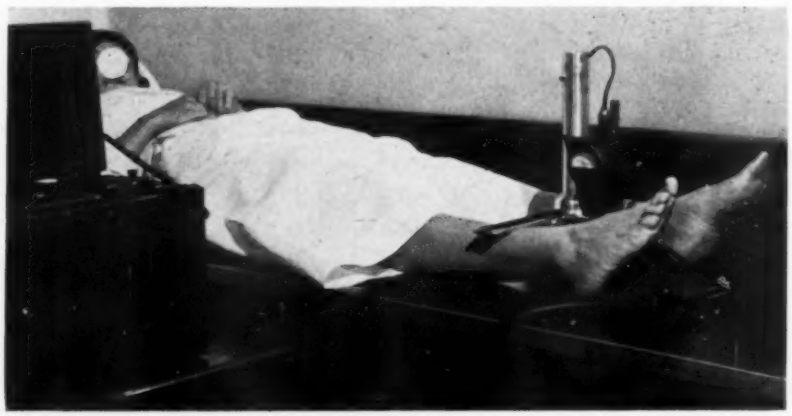

Fig. 1.—Illustration of recording of ballistocardiogram (photocell displacement type) with patient recumbent on firm wood table. The tracing is taken simply with a single-channel electrocardiograph.

We examined, consecutively, a group of 350 patients, including normal controls and patients with suspected, as well as definitely proved, heart disease. For the purpose of this report, analysis was made of eighty of the cases belonging to the group of normal subjects.

With the photocell displacement method employed in this study, as with that of Starr and Nickerson, four classical waves of the ballistocardiogram may be identified, the H, I, J, and K waves (see Fig. 2). Headward motion of the body is recorded as an upward movement of the cardiographic beam and vice versa. The H, or initial headward movement, has been related to the apical thrust with early systole by some authors,[7] and to auricular contraction by others.[8] An earlier footward deflection, the G wave, has recently been identified with auricular contraction in records taken with the low-frequency, critically damped Nickerson apparatus.[9] The H is normally followed by a footward movement, the I wave, which represents the recoil from ejection of blood from

the heart into the ascending aorta and pulmonary arteries. The J wave, the next headward deflection, is related to the impact of blood against the aortic arch and pulmonary artery bifurcation and recoil from the footward acceleration of blood in the aorta. The succeeding footward movement, the K wave, results from the rapid deceleration of blood in the descending aorta and impact with small peripheral arteries. The remaining deflections are labelled L, M, N, O, etc. waves in alphabetical order and may represent aftervibrations (with the natural frequency of the body resulting from the initial impacts described) or actual forced thrusts.

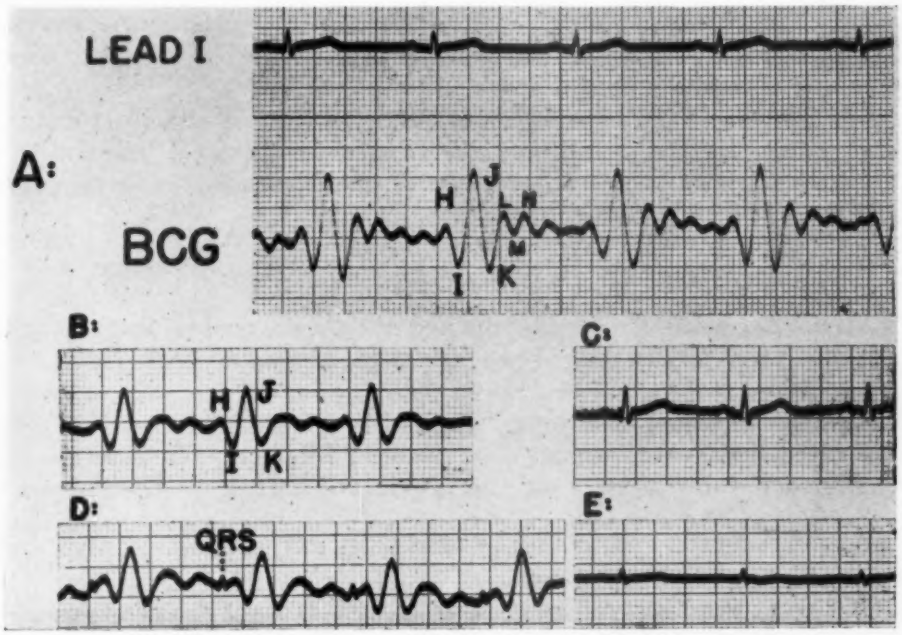

Fig. 2.—K. C., a normal young man, 28 years old. *A*, Simultaneous tracing of Lead I of the electrocardiogram and normal ballistocardiogram (at held slight inspiration) on multi-channel machine. *B*, *C*, *D*, and *E* tracings were taken on a single-channel machine. *B*, Normal ballistocardiogram; *C*, Lead I normal standardization; *D*, combined ballistocardiogram and electrocardiogram (Lead I understandardized for time reference); *E*, Lead I, understandardized as in *D*.

Ballistocardiographic tracings are classified as to normality on a qualitative basis, depending upon the contours of the various component waves. Normal records are of "W"-shaped appearance, as illustrated in Fig. 2. In normal subjects the amplitude of the I wave is slightly less than that of the K wave, and the J wave is the most prominent headward deflection. Criteria for abnormality of the ballistocardiogram include the following: definite slurring or notching of the I, J, or K waves; marked relative diminution in amplitude or absence of I waves; prominent H wave (early "M" pattern); late, deep notching of the J wave (late "M" pattern); prominent L or other diastolic waves; deep, widened, or absent K waves; and, finally, low amplitude or completely bizarre tracings, with indistinguishable wave forms. These alterations from normal may appear in various combinations in the same record.

The phase of respiration bears a definite relationship to the appearance of the ballistocardiogram. Usually, the patterns are similar qualitatively in quiet respiration as compared with tracings in deep inspiration and deep expiration. Quantitative ballistocardiographic changes occur normally with respiration and are related to the increased cardiac output with inspiration and the decreased output with expiration. Prominent respiratory variation in amplitude, i.e., marked diminution in expiration as compared with inspiration, is abnormal. Records which are normal in contour during quiet respiration and deep inspiration, but occasionally abnormal in another phase, such as deep expiration, have been noted and have been considered borderline for the present. It is important to realize that artifacts may occur; tracings which show only a rare abnormal curve are still considered basically normal.

It is significant that, in ballistocardiography, the results obtained by any one method are not necessarily identical with those of any of the alternate methods described. The conflicting observations in cases of coarctation of the aorta with the different methods are exemplary in this regard.

RESULTS

Normal Subjects.—This group consisted of eighty normal patients, sixty-two male and eighteen female, ranging in age from 18 to 64 years. All were asymptomatic and presented normal findings on physical examination. Blood pressure, cardiac fluoroscopy and/or roentgenograms of the chest, and twelve-lead resting electrocardiograms were normal. The double "Master 2-step" exercise electrocardiogram[10] was assayed in the entire group, and the tests were negative in all.

Ballistocardiogram at rest: The results of ballistocardiographic tracings in these normal patients showed normal records, at rest, in seventy of the eighty subjects (Fig. 2), including twenty-nine who were 50 years of age or over (Table I). Abnormal ballistocardiographic tracings at rest were found in seven subjects, five of whom were 50 years of age or over. Three records were borderline at rest in the older age group.

TABLE I. NORMAL CONTROLS AND RESTING BALLISTOCARDIOGRAM*

AGE	NO. CASES	RESTING BCG		
		NORMAL	ABNORMAL	BORDERLINE
Under 50 years	44	41	2	1
50 years and over	36	29	5	2
Totals	80	70	7	3

*Normals all presented negative physical examination, normal blood pressure, chest fluoroscopy, and resting electrocardiogram, and negative double "2-step" exercise electrocardiograms.

Ballistocardiogram after exercise: The ballistocardiogram was recorded both before and immediately after the double "2-step" exercise in sixty-three of the eighty normal patients (Table II). In this group, the resting ballistocardio-

gram was normal in fifty-three, abnormal in seven, and borderline in three. Of the fifty-three normal subjects with negative resting ballistocardiograms, the ballistocardiogram after the double "2-step" test remained normal in forty-eight and became abnormal in three and borderline in two. Of the seven with abnormal resting ballistocardiograms, the ballistocardiogram after the double exercise test remained abnormal in six and became normal in one. The abnormalities noted in the ballistocardiogram at rest in this group were similar to those after exercise and consisted of very small or absent I waves. Ballistocardiographic alterations related to body habitus (such as in normal pyknic and obese patients) are being analyzed at present.

TABLE II. NORMAL CONTROLS AND EXERCISE BALLISTOCARDIOGRAM

NORMAL CONTROLS	BCG AT REST		EXERCISE BCG		
			NORMAL	ABNORMAL	BORDERLINE
Double "2-step" ECG negative 63	Normal:	53	48	3	2
	Abnormal:	7	1	6	0
	Borderline:	3	0	2	1
Totals 63		63	49	11	3

DISCUSSION

By the new method of recording ballistic impulses from the body with the photocell displacement type of apparatus (modified after Dock), ballistocardiography has become a simple clinical procedure for the routine study of cardiac patients. Theoretical objections to this method, such as lack of critical damping, extreme variation in body habitus and in body frequency, and so forth, are in large measure overruled by weight of clinical correlation. Furthermore, such objections are partially eliminated when comparative tracings are taken in the *same* individual at rest and after standard exercise.

For the average tracings, ballistocardiographic records taken on single-channel electrocardiographic machines are adequate and may be interpreted with facility. With the multiple-channel electrocardiographic machine, cardiac recordings, such as the phonocardiogram, electrocardiogram, and pulse tracings, may be made simultaneously with the ballistocardiogram; these serve as an invaluable aid in interpretation of the results, especially in bizarre records. With single-channel machines, such as those employed in everyday clinical practice, electrocardiographic and ballistocardiographic tracings may be recorded simultaneously, simply by connecting both in series or parallel.[14] The resultant superimposition of tracings with this method serves for accurate time reference of the component waves of the ballistocardiogram. Simple regulation of the standardization control allows for relative diminution of the electrocardiographic pattern in relation to the ballistocardiographic waves, and, thus, the former distorts the latter only minimally (Fig. 2,*D*). Successive recording of the ballistocardiogram alone then serves for more precise interpretation.

In the analysis of the results in the normal group, it is important to emphasize the actual criteria utilized in the selection of subjects. In order to be considered normal, the individual chosen must be asymptomatic and must present normal findings on physical examination, blood pressure, cardiac fluoroscopy, and routine twelve-lead resting electrocardiograms. Since the resting electrocardiogram may be normal in from 25[11] to 37[10] per cent of patients with angina pectoris due to coronary artery disease, the aforementioned criteria alone are, obviously, inadequate for the determination of normality. Therefore, we accepted the patient as normal for this study only if, in addition, the *double* Master "2-step" exercise electrocardiogram test was found to be negative.

In the group of forty-four normal subjects below the age of 50 years, the results with the ballistocardiogram showed good correlation with the normal clinical criteria. In the group of thirty-six subjects, 50 years of age and over, five showed definitely abnormal resting ballistocardiograms. In the interpretation of this finding, one must consider the possibility that these five "normal" subjects represent cases of subclinical cardiovascular disease (as shown in follow-up studies reported by Starr[12] and Makison[13]). One should remember that abnormal ballistocardiograms are related to abnormal cardiac and/or abnormal peripheral vascular states. The increasing vascular sclerosis with advancing age may account for the abnormal ballistocardiographic tracings in the older age group of normal subjects.[14,15] Therefore, a *normal* ballistocardiogram in the older patient may be of diagnostic significance, indicating a normal cardiac and peripheral vascular state, whereas an *abnormal* one in the aged should be interpreted with the utmost caution. Complete follow-up studies are being conducted in all cases in order to determine further the significance of the findings reported.

SUMMARY

1. The ballistocardiogram, as recorded by the photocell displacement apparatus (modified after Dock), was investigated in a consecutive group of eighty normal control subjects.

2. In the series of normal subjects, the ballistocardiogram was found to be normal at rest in seventy, abnormal in seven, and borderline in three. The significance of these findings has been discussed.

3. Of fifty-three normal controls with normal resting ballistocardiograms who were exercised, the ballistocardiogram in forty-eight remained normal after the double "2-step" test. A careful follow-up study of the normal subjects with abnormal ballistocardiograms will be made in order to determine the clinical implication of these findings.

4. The unhinged photocell displacement ballistocardiogram apparatus was employed with a simple method for simultaneous recording of the electrocardiogram with the commonly employed single-channel cardiographic machines.

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CLINICAL EVALUATION OF THE BALLISTOCARDIOGRAM

II. Heart Disease—Hypertension, Angina Pectoris, and Myocardial Infarction

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WITH the introduction of the apparatus for recording ballistocardiograms directly from the body, Dock and Taubman[1] devised another simple clinical procedure for the investigation of cardiovascular disease. In order to evaluate this procedure, we undertook study of normal controls[2] as well as of patients with known cardiac disease. Thus far, 350 subjects have been examined. For the purposes of this report, the findings in 3 major groups of patients will be analyzed: (1) hypertensive patients, (2) patients with normal resting electrocardiograms, but with positive Master "2-step" exercise tolerance tests, and (3) patients with previous myocardial infarction—a total of 135 cases.

Most of the investigations in the field of ballistocardiography in the past decade have been performed with the high-frequency, undamped Starr apparatus[3] or the low-frequency, critically damped Nickerson table.[4] It seemed advisable, therefore, to study empirically a large series of patients with a simple, practical apparatus, in order to evaluate its role as a routine clinical diagnostic method in the field of cardiology.

METHOD

For this study, we employed the photocell displacement type apparatus, as described by Dock[1] and modified by us.[2] The patients were placed horizontally upon a rigid, immobile wood table, and the records were obtained directly from the body. When abnormal tracings are seen, especially those which are bizarre, simultaneous cardiac phenomena may be recorded for time reference. With multiple-channel or even single-channel machines,[2] simultaneous records of ballistocardiograms and electrocardiograms may be taken simply. Phonocardiograms or pulse tracings may also be utilized for time reference.

RESULTS

1. Hypertensive Patients.—This group consisted of 50 patients, 40 with clinical evidence of hypertensive heart disease and 10 with essential hypertension; 23 were male and 27 female, ranging in age from 34 to 77 years. Thirty-six

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patients were 50 years of age or over. The routine twelve-lead electrocardiogram showed normal tracings in 18 patients, left ventricular "strain" patterns in 28, previous infarction (alone and in addition) in 4, and T-wave abnormalities in 2.

The ballistocardiogram at rest was abnormal in 38 of the 40 patients with hypertensive heart disease and borderline in one (Table I). The abnormalities most frequently encountered were a combination of very small or absent I waves and deep K waves (21 cases) (Fig. 1,*A*). Small or absent I waves occurred alone in 9 cases, deep K waves alone in 4, bizarre patterns in 2, and a combination of small I wave and bizarre patterns in the remaining 2 cases. The patient with the borderline ballistocardiogram displayed a normal pattern on slight inspiration and absent I waves on deep inspiration. Only one hypertensive patient was found to have a normal ballistocardiogram at rest. He presented a clinical picture of early hypertensive heart disease with angina pectoris, slight left ventricular enlargement, blood pressure of 155/110 mm. Hg, and a typical left ventricular "strain" type of electrocardiogram. The ballistocardiogram remained normal even after performance of the double "2-step" test.

TABLE I. HYPERTENSIVE HEART DISEASE AND RESTING BALLISTOCARDIOGRAM

ECG AT REST	RESTING BCG		
	NORMAL	ABNORMAL	BORDERLINE
Normal: 8	0	8	0
Abnormal: 32	1	30	1
Total hypertensives: 40	1	38	1

The 10 patients with essential hypertension all had normal resting electrocardiograms. The resting ballistocardiogram was abnormal in 9 cases and normal in one. The abnormalities consisted of a combination of a tiny I and deep K in 5 cases, tiny I in 3, and a deep K in one.

Eleven of the 18 hypertensive patients with normal resting electrocardiograms were studied after performance of the double "2-step" exercise test. The "2-step" electrocardiogram test was negative in 8 cases, borderline in 2, and positive in one; the ballistocardiogram after exercise, however, remained abnormal in all 11 instances. The hypertensive patient with the positive double "2-step" electrocardiogram test suffered from angina pectoris; the abnormal resting ballistocardiogram and elevated blood pressure were normalized after intravenous injection of 0.5 mg. of Dihydroergocornine (DHO-180),[5] a "sympathicolytic" drug.

In summary, in 10 patients with essential hypertension and 40 with hypertensive heart disease, only 2 were found to have a completely normal ballistocardiogram at rest.

2. Patients With Normal Resting Electrocardiograms, but Positive Response to the Master "2-Step" Test.—This group consisted of 45 patients, 26 male and 19

female, ranging in age from 29 to 70 years; 32 patients were 50 years of age or over. Forty patients gave histories of angina pectoris (typical or atypical). The remaining 5 patients included 2 on the psychosomatic service, one hypertensive, one hyperthyroid, and one case of neurocirculatory asthenia. The routine twelve-lead electrocardiogram was normal in all 45 patients. The Master "2-step" electrocardiogram test[6] was positive in all 45 cases, in 12 instances with the single test and in the remaining 33 with the double test.

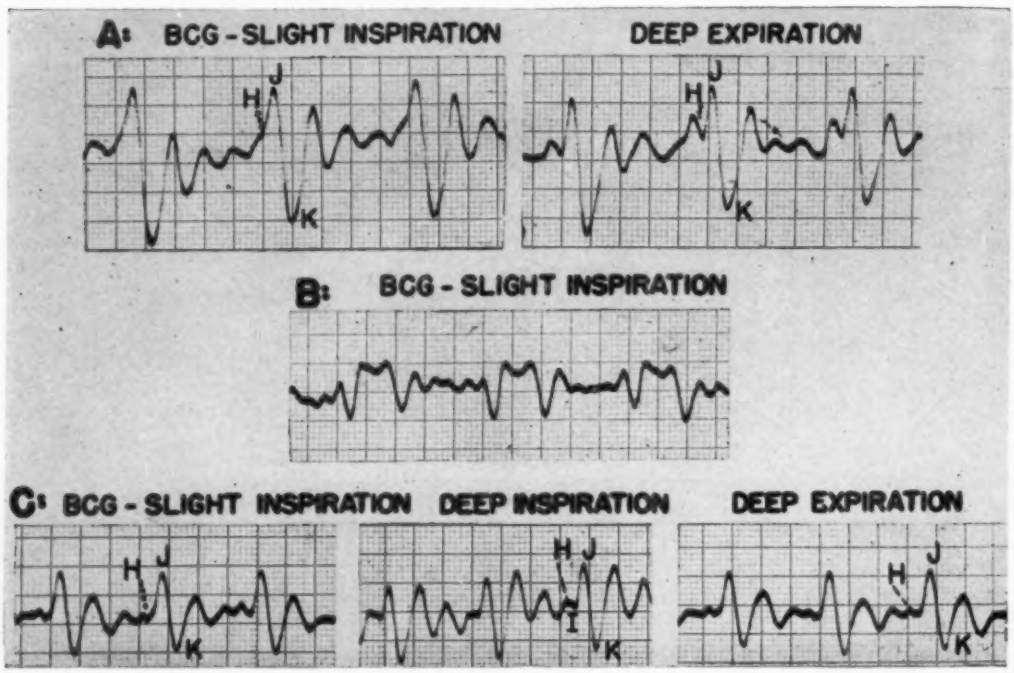

Fig. 1.—*A*, J. J., No. 203, male, 45 years old, had hypertensive heart disease with a blood pressure of 230/130 mm. Hg. There was a left ventricular "strain" electrocardiogram pattern and an enlarged left ventricle. The ballistocardiogram was abnormal at rest, with a small H, absent I, and deep, wide K wave.

B, L. Z., No. 50, male, 47 years old, had coronary occlusion for three years. The electrocardiogram showed an old anteroseptal infarction. The resting ballistocardiogram was abnormal with a bizarre "M" pattern.

C, J. H., No. 181, male, 48 years old, had coronary artery disease and angina pectoris. Physical examination, fluoroscopy, blood pressure, and resting electrocardiogram were all normal, but the double "2-step" electrocardiogram was abnormal. The ballistocardiogram at rest was abnormal with small to absent I waves.

The resting ballistocardiograms were normal in 10 patients, borderline in one, and abnormal in 34 of the group (Table II). The alterations consisted of very small or absent I waves in 25 of the 34 abnormal resting ballistocardiograms (Fig. 1,*C*); the remainder showed abnormal J-K segments and bizarre patterns. In the angina group (with normal resting electrocardiograms and positive "2-step" tests), the ballistocardiogram at rest was abnormal in 30 of the 40 patients.

The ballistocardiogram was recorded after the "2-step" exercise test in 21 of this group of 45 cases. Of these, 2 were normal and 19 abnormal (Table III). Only 6 of the 10 patients with a normal ballistocardiogram at rest were exercised.

Four of these showed abnormalities after the "2-step" test. The patient with a borderline ballistocardiogram at rest displayed an abnormal tracing after exercise. No abnormal resting ballistocardiogram in this group reverted to normal following exercise.

TABLE II. RESTING BALLISTOCARDIOGRAM AND POSITIVE "2-STEP" ELECTROCARDIOGRAM TESTS

DIAGNOSIS	NORMAL ECG AT REST	BCG AT REST			POSITIVE "2-STEP" ECG TEST	
		NORMAL	ABNORMAL	BORDERLINE	SINGLE	DOUBLE
Angina pectoris and/or coronary insufficiency	40	9	30	1	11	29
Neurocirculatory asthenia	1	1	0	0	0	1
Psychosomatic cases	2	0	2	0	0	2
Hypertension	1	0	1	0	1	0
Hyperthyroidism	1	0	1	0	0	1
Total	45	10	34	1	12	33

TABLE III. EXERCISE BALLISTOCARDIOGRAM AND POSITIVE "2-STEP "TESTS

DIAGNOSIS	NORMAL ECG AT REST AND POSITIVE "2-STEP" ECG	BCG AT REST		BCG AFTER EXERCISE	
				NORMAL	ABNORMAL
Angina pectoris and/or coronary insufficiency	19	Normal:	5	1	4
		Abnormal:	13		13
		Borderline:	1		1
Neurocirculatory asthenia	1	Normal:	1	1	
Hyperthyroidism	1	Abnormal:	1		1
Total	21		21	2	19

Thus, the ballistocardiogram in 45 patients (with positive exercise electrocardiograms and negative resting electrocardiogram tracings) showed abnormal patterns at rest in over 75 per cent of the cases (34 patients); 5 of the 7 remaining subjects studied showed definite ballistocardiographic abnormalities only after standard exercise tests.

3. Previous Infarction.—This group was comprised of 40 patients with previous myocardial infarction. There were 29 male and 11 female patients, ranging in age from 25 to 78 years. The diagnosis of infarction was substantiated by the clinical course and the electrocardiographic evidence. At the time of the present examination, the electrocardiogram was normal in 4 patients and definitely abnormal in the remaining 36. In all of the 4 patients with normal electrocardiograms, the ballistocardiogram at rest was abnormal. In the 36 patients with abnormal electrocardiograms, the ballistocardiograms at rest were normal

in 3 and abnormal in 33 (Table IV). The abnormalities of the ballistocardiograms consisted of very small or absent I waves in 23 cases, small I waves with delayed J-K segments in 5, late "M" patterns in 5 (Fig. 1,*B*), delayed J-K segments in 3, and a bizarre pattern in one. In summary, of 40 patients with previous myocardial infarction, the ballistocardiograms at rest were abnormal in 37.

TABLE IV. PREVIOUS MYOCARDIAL INFARCTION AND RESTING BALLISTOCARDIOGRAM

ECG AT REST		RESTING BCG	
		NORMAL	ABNORMAL
Normal:	4	0	4
Abnormal:	36	3	33
Total	40	3	37

DISCUSSION

The empirical findings of this preliminary investigation further attest to the practical value of the procedure studied. In our analysis of the records, emphasis has been placed on the qualitative appearance of the various component waves of the ballistocardiogram.

Since quantitative determinations of cardiac output by this method of ballistocardiography are inadequate, its application for purposes of exact measurement of physiological phenomena is limited. However, the qualitative appearance of ballistocardiographic tracings has aided in the differential diagnosis of normal subjects from those with cardiac disease, on an empirical basis alone. Thus, as in electrocardiography, experience allows normal patterns to be readily distinguished from abnormal ones. It must be remembered that ballistocardiographic patterns evolve from *mechanical* cardiovascular events and that electrocardiographic tracings represent *electrical* cardiac potentials. Therefore, no one-to-one correlation between normal and abnormal ballistocardiograms and electrocardiograms is predicted or expected. However, a knowledge of the relative merits of each method is exceedingly valuable and serves as the principal purpose of this preliminary report. The fact that the underlying theoretical basis of this procedure has remained unsolved in no way limits the value of the findings reported.

The most frequent ballistocardiographic alterations encountered in the abnormal cases were very small or absent I waves. It has been found that this abnormality, as well as the others described above, is not specific for any one particular cardiovascular disease entity. Therefore, this fact should be borne in mind when one applies the finding of an abnormal ballistocardiogram tracing to a specific clinical case. The finding of abnormal ballistocardiogram tracings in the hypertensive group and the reversal of the ballistocardiogram to normal in

some of these patients with DHO-180 (Dihydroergocornine) would tend to indicate that the associated peripheral vascular phenomena may be responsible for the abnormal ballistocardiogram tracings.

SUMMARY

1. Analysis of ballistocardiographic tracings has been made in a group of 135 subjects with known cardiac disease.

2. In the patients with essential hypertension and hypertensive heart disease, only 2 were found to have a completely normal ballistocardiogram at rest.

3. Seventy-five per cent of the angina patients with negative resting electrocardiograms (and positive exercise electrocardiogram tests) showed abnormal ballistocardiographic patterns at rest. Of 5 angina patients with normal resting ballistocardiograms, the ballistocardiogram in 4 became abnormal only after exercise.

4. The ballistocardiogram was abnormal at rest in over 92 per cent of the patients with previous myocardial infarction.

5. Preliminary confirmatory evidence of the valuable aid of the ballistocardiogram in everyday clinical practice is presented.

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POSTOPERATIVE CHANGES IN CARDIAC OUTPUT

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DURING the past three years, patients have been studied intensively from the standpoint of fluid, electrolyte, nitrogen, and caloric balance in the Surgical Metabolism Unit of the Presbyterian Hospital. Other physiological changes incident to operation have been recorded, among which is the cardiac output. This report records the study of cardiac output in the pre- and postoperative periods, as it varies with the condition of the patient, type of operation, and therapy.

Starr and Mayock,[1] in 1945, recorded observations on cardiac output in relation to operation employing the high-frequency ballistocardiograph and noted that following simple herniorrhaphy, with the patient in the horizontal position, there was a decrease in cardiac output. In the more major operations, the same was true except when the patients received large amounts of fluids intravenously or when there was a larger protein and caloric intake. No significant difference was noted in cardiac output between patients having a herniorrhaphy who were kept at bed rest and those who exercised in bed or were allowed to walk early. However, the patients were first studied on the sixth postoperative day, and earlier changes might have been missed. Mayock and associates,[2] in 1946, reported from the same clinic on patients undergoing more serious operations, having a ballistocardiographic tracing made immediately, one, two, five, and ten days postoperatively. They noted that the average cardiac output was never significantly different from the value found before operation and that those patients in nitrogen equilibrium had less abnormality of the circulation after operation than those in negative balance. Hardy and Godfrey,[3] in 1944, employing Starr's ballistocardiograph measured the change in cardiac output in dehydrated patients given fluids intravenously and observed a significant increase, whereas such changes were not observed in the normal controls.

METHODS

Of the total of fifteen patients studied, thirteen were in the metabolism unit and two on the general ward service. The thirteen were on nitrogen, electrolyte, and fluid balance studies and were weighed daily. Diets were obtained from a special kitchen serving the unit only. Nitrogen analyses were performed by the

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TABLE I.

TABLE I.

PATIENT	DATE	WEIGHT (KG.)	DAILY N_2 BALANCE	CUMULATIVE N_2 BALANCE	HTC (%)	TBV (C.C.)	BMR (%)	RECTAL TEMP. (8 A.M.)	BP (MM. Hg)	SV (C.C.)	HR	CI	I. V. FLUIDS (C.C.)	BCG PATTERN
C. S.	10/28	70.2	+ 0.5	+ 0.5	44	5940		99.2	110/75	65	63	2.2	0	Normal
50 year, male, hernia,	11/3	69.9	+ 0.4	+ 3.8	45	6060		98.2	105/70	62	55	1.8	0	Normal
11/8	11/9	69.3	− 0.2	+ 4.8	43			99.0	110/80	50	70	1.9	0	Normal
	11/10	69.5	− 2.1	+ 2.7	42			98.8	105/75	47	66	1.6	0	Normal
	11/12	69.8	+ 1.8	+ 5.0	43	5790		99.2	105/70	46	59	1.4	0	Normal
	11/15	69.5	+ 1.7	+ 9.0	40			98.0	100/65	47	62	1.5	0	Normal
F. S.	11/23	61.2	− 1.4	− 1.4	46			98.0	100/60	92	58	3.1	0	Slight bowing of the JK segment
18 year, male,	11/24	60.8	− 1.4	− 2.8	45	4870		98.0	95/55	90	58	3.1	0	Slight bowing of the JK segment
hernia,	11/30	59.8	− 4.4	−14.5	43			98.0	100/60	86	57	2.9	0	Slight bowing of the JK segment
12/3	12/1	60.0	− 4.3	−18.8	44	4690		98.0	100/60	78	56	2.5	0	Slight bowing of the JK segment
	12/4	58.5	− 6.6	−29.4	40			99.0	105/60	99	68	3.9	0	Slight bowing of the JK segment
	12/5	58.0	− 0.4	−29.8	43			99.0	105/65	86	61	3.1	0	Slight bowing of the JK segment
	12/7	58.0	− 0.9	−31.4	42	4230		98.4	95/60	83	58	2.9	0	Slight bowing of the JK segment
	12/10	57.5	− 3.9	−41.2	40			98.0	95/55	80	54	2.5	0	Slight bowing of the JK segment
T. L.	7/13	58.3	− 1.8	− 1.8	44	6150		98.6					0	
35 year, male,	7/20	57.4	0.0	−21.3	45	5490		98.6					0	
hernia,	7/21	57.3	− 7.1	−28.4	42			98.6	85/60	87	60	3.1	0	Normal
7/22	7/22												3077	
	7/23	57.1	+ 0.7	−28.8	40			100.0	110/70	145	66	5.7	0	Normal
	7/24	57.0	− 5.4	−34.2	40			99.0	110/65	124	65	4.8	0	Normal
	7/26	57.5	− 2.5	−37.9	36			98.8	90/60	99	59	3.4	0	Normal
	7/29	57.6	+ 0.7	−38.9	38			98.8	95/60	99	60	3.5	0	Normal
R. W.	10/12							98.8	100/65	96	63	3.7	0	Normal
20 year, male, thyroidectomy,	10/13							98.6	100/70	80	63	3.1	1500	Normal
10/13	10/14							99.6	95/65	88	62	3.2	0	Normal
	10/15							99.6	100/65	88	69	3.7	0	Normal
	10/17							99.0	95/65	81	53	2.7	0	Normal

HTC = hematocrit
TBV = total blood volume
BMR = basal metabolism rate
BP = blood pressure
SV = stroke volume
HR = heart rate
CI = cardiac index

TABLE II.

PATIENT	DATE	WEIGHT (KG.)	DAILY (N_2 BALANCE	CUMULATIVE N_2 BALANCE	HTC (%)	TBV (C.C.)	BMR (%)	RECTAL TEMP. (8 A.M.)	BP (MM. Hg)	SV (C.C.)	HR	CI	I. V. FLUIDS (C.C.)	BCG PATTERN
J. B.	3/19	77.5			47			98.0	95/70	46	65	1.5	0	Slight bowing of the JK segment
47 year, male, subtotal gastrectomy, 3/23	3/21	77.4	− 1.6	− 1.6	48			97.8	95/65	34	66	1.2	0	Slight bowing of the JK segment
	3/23												3300	
	3/24	75.5		− 3.5	50			100.6	105/80	26	106	1.4	2465	Slight bowing of the JK segment
	3/25	74.7	−16.5	−20.0				100.0	110/75	30	100	1.6	1491	Slight bowing of the JK segment
	3/27	73.5	− 7.3	−39.7	44			99.4	100/70	36	87	1.6	0	Slight bowing of the JK segment
	3/30	73.3	− 2.4	−53.2	44			98.0	100/65	41	79	1.7	0	Slight bowing of the JK segment
T. H.	12/1	51.4	+ 2.3		40			99.2	105/65	80	53	2.7	0	Normal
41 year, male, subtotal gastrectomy, 12/3	12/2	51.2			37			98.4	110/70	79	60	3.0	0	Normal
	12/3												2542	
	12/4	52.3			39			100.6	115/75	96	71	4.4	2000	Normal
	12/5	51.4			38			100.0	115/75	86	70	3.8	974	Normal
	12/7	50.5			33			99.0	110/70	75	60	2.8	0	Normal
	12/9												500	
	12/10	51.0						98.4	115/75	72	49	2.2	0	Normal
L. H.	3/28	85.8	− 1.3	− 1.3	47		− 9	98.0	120/75	59	79	2.3	0	Normal
59 year, male, subtotal gastrectomy, 3/30	3/29	85.5	− 3.3	− 4.6	45		− 2	98.0	120/75	70	76	2.6	0	Normal
	3/30												1966	
	3/31	83.3		−11.5	56		+29	100.4	135/80	93	89	4.1	1500	Normal
	4/1												1990	
	4/2												1985	
	4/3	83.5	−15.9	−49.6			+22	100.0	140/80	89	91	4.0	0	Normal
	4/6	82.1	− 5.4	−73.3	43		+42	98.0	120/70	80	81	3.2	0	Normal

F. C.	2/8											3320	
60 year, male,	2/9	59.7	− 4.4	− 4.4	38			99.0				5953	
subtotal	2/10											5956	
gastrectomy,	2/14	61.0	+ 1.8	−19.8	35			98.2	110/60	58	78	2.5	0	Marked bowing of the JK segment
2/16	2/15	60.8	− 3.4	−23.2	35		+11	98.2	95/60	58	72	2.4	740	Marked bowing of the JK segment
	2/16	60.5	− 0.7	−23.9	36		+84	98.4	110/65	64	73	2.6	3228	Marked bowing of the JK segment
	2/17	60.0	− 8.8	−32.7	41		+74	100.6	125/70	84	98	4.6	1984	Normal
	2/18	59.5	− 9.3	−42.0	42		+12	100.2	120/65	58	92	3.0	975	Normal
	2/20	58.4	− 8.3	−61.0	42		+60	98.2	105/60	60	70	2.4	0	Normal
	2/23	57.3	− 7.9	−73.4	42		+88	98.2	105/60	60	63	2.2	0	Normal
P. C.	5/20	64.5					+ 7	98.0	100/70	84	68	3.3	0	Slight bowing of the JK segment
39 year, male,	5/21	64.5	− 2.5	− 2.5				98.2					0	
subtotal	5/23	64.5	+ 3.0	+ 5.9			+ 7	98.4	100/70	86	62	3.1	0	Slight bowing of the JK segment
gastrectomy,	5/24	65.0	+ 4.7	+10.6	52		+ 7	98.2	105/70	82	75	3.6	1693	Slight bowing of the J-K segment
5/25	5/25	64.0	−11.1	− 0.5	49		+45	98.2	110/70	84	79	3.9	2000	Slight bowing of the K segment
	5/26	62.4	− 6.9	− 7.4	48		+52	100.0	130/80	106	72	4.5	1979	Normal
	5/27	62.4	−10.1	−17.5	45		+21	100.6	135/85	110	70	4.5	2672	Normal
	5/29	62.5	− 8.9	−28.4			+12	99.2	110/75	86	65	3.3	0	Normal
	6/1	62.1	− 9.5	−36.6	46		+ 5	98.0	110/70	82	71	3.5	0	Normal
W. M.	10/16							99.0	80/60	57	59	2.0	500	Normal
54 year, male,														
subtotal	10/18							98.4	95/70	73	64	2.8	1500	Normal
gastrectomy,	10/19							99.4	115/70	100	59	3.4	1000	Normal
10/18	10/20							99.4	120/75	75	70	3.1	3500	Normal
	10/21												1000	
	10/22							99.8	100/60	51	54	1.6	0	Normal
	10/25							98.0	105/70	57	52	1.8	0	Normal

HTC = hematocrit
TBV = total blood volume
BMR = basal metabolism rate
BP = blood pressure
SV = stroke volume
HR = heart rate
CI = cardiac index

micro-Kjeldahl method,[4] sodium and potassium ions using an internal standard flame photometer as developed by Barnes and co-workers,[5,6] and chlorides by the method of Schales and Schales.[7] Blood volumes were determined using the blue dye T-1824, as described by Gregersen.[8]

The observations made on the cardiovascular system included blood pressure, heart rate, and the ballistocardiogram. The blood pressure was recorded by sphygmomanometer and the heart rate from the electrocardiogram recorded simultaneously with the ballistocardiogram. From the latter the stroke volume (c.c. per stroke) and the cardiac index (liters per minute per square meter) were computed. The ballistocardiograph used in this study was the low-frequency, critically damped instrument designed by Nickerson and Curtis[9] and calibrated against the direct Fick method by Nickerson, Warren, and Brannon.[10] On the basis of the comparison with the Fick method, a relative change greater than 15 per cent in the cardiac index or stroke volume is considered significant. All measurements were made on records taken over a one-half hour period following an equal period of absolute rest on the ballistocardiograph. All patients fasted at least ten hours. The stroke volume and cardiac index measurements were made from records taken during normal respiration. Basal metabolic rates were determined with a Benedict-Roth apparatus in seven patients. These observations were made on several days during the ten-day period preceding the operation and postoperatively were made in the early morning of the first, second, fourth, and seventh days following the operation.

RESULTS

The fifteen patients may be grouped according to the type of operation. Group 1 (Table I) is composed of four patients, three of whom (C. S., F. S., and T. L.) were in the metabolism unit and had unilateral inguinal herniorrhaphies. The fourth (R. W.) had a partial thyroidectomy for nontoxic nodular goiter and was on the general ward service. The diets of the three patients in the unit contained 85 Gm. of protein daily given either by mouth or intravenously (as a 10 per cent amino acid solution*). The caloric intake of patients F. S. and T. L. was reduced preoperatively according to the program of the metabolism study in which they were included and accounted for the negative nitrogen balances noted in the table. None of the four had previous weight loss. All operations were performed by the resident staff. The anesthetic agents used were thiopental sodium and nitrous oxide.

Group 2 (Table II) is composed of six patients (J. B., T. H., L. H., F. C., P. C., and W. M.). There was great variability as to the daily intake of nitrogen and calories before operation, but all were on an ambulatory ulcer diet. T. H. and W. M. had lost about 10 pounds in weight in the previous year and F. C. 10 pounds in the two weeks before hospital admission. The other three had no previous weight loss. All had chronic duodenal ulcers and underwent a subtotal gastrectomy under cyclopropane anesthesia. The diet following operation consisted of nothing by mouth the day of operation, 100 ml. of water by mouth every

*Supplied by Merck & Company, Inc., Rahway, N. J.

hour while awake the first postoperative day, 100 ml. of clear liquid every hour the second day, 100 ml. of full liquids the third day, a soft diet in six small feedings the fourth and successive postoperative days.

Group 3 (Table III) is composed of five patients (W. H., A. L., E. F., P. S., and C. Q.), all of whom had a cholecystectomy for chronic cholecystitis and cholelithiasis under cyclopropane anesthesia. While the protein intake by mouth or vein was constant at 85 Gm, there was variability as to the route and the amount of caloric intake. None in this group had previous weight loss.

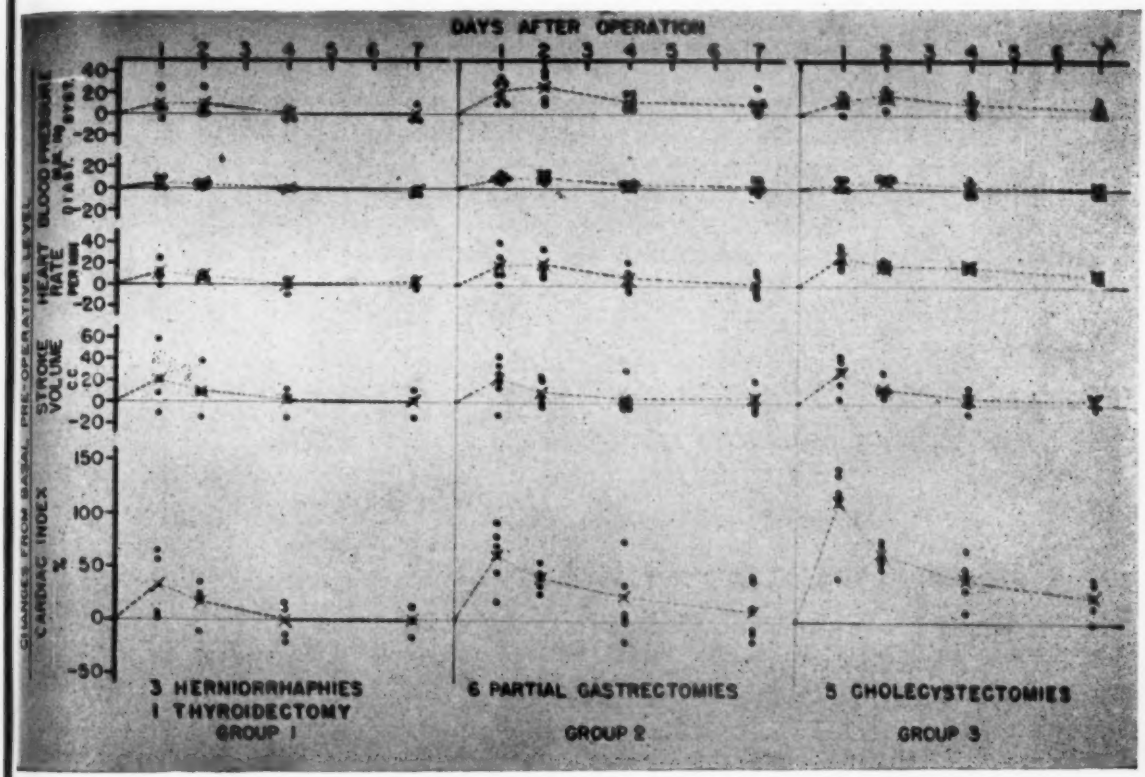

Fig. 1.—The mean postoperative changes of blood pressure, heart rate, stroke volume, and cardiac index from the preoperative levels are shown by the dotted lines in the figure. X's represent mean values, and the filled black circles represent individual patients. Patients are grouped according to type of operation.

The patients in all three groups walked ten minutes beginning the first postoperative day and progressed in succeeding days.

The results of the cardiovascular measurements are recorded in Tables I, II, and III and are represented graphically in Fig. 1. The basal preoperative levels of Fig. 1 represent the average of from six to twelve observations recorded during the preoperative period. Each data point in the figure is the average of three observations. The grouping by type of operation coincided closely with the relative progress in convalescence. Group 1 exhibited the shortest, Group 2 an intermediate, and Group 3 the most prolonged recovery period.

TABLE III.

PATIENT	DATE	WEIGHT (KG.)	DAILY N_2 BALANCE	CUMULATIVE N_2 BALANCE	HTC (%)	TBV (C.C.)	BMR (%)	RECTAL TEMP. (8 A.M.)	BP (MM. Hg)	SV (C.C.)	HR	CI	I. V. FLUIDS (C.C.)	BCG PATTERN
W. H.	2/19	76.0	− 1.1	− 1.1	47.0	5850		99.0					0	
43 years, male,	2/26												5037	
chole-	2/27												5021	
cystectomy and	2/28	75.0	− 2.9	−14.6	45.0	5940	− 1	98.0	105/65	65	82	2.8	5023	Slight bowing of the JK segment
appendectomy,	3/1												5026	
3/9	3/2	74.1	− 2.5	−22.1			− 3	98.4	110/75	60	84	2.6	0	Slight bowing of the JK segment
	3/3	74.5	− 0.2	−22.3	41.5	5690	− 7	99.4	110/70	58	72	2.1	0	Normal
	3/8	74.3	− 0.7	−24.8	42.0		+ 1	98.2	100/65	73	62	2.4	0	Normal
	3/9	74.6	− 0.7	−25.5	44.0		− 3	98.2	110/70	71	70	2.6	4980	Normal
	3/10	74.3	− 2.7	−28.2	43.0			99.6	110/70	98	97	5.0	4216	Normal
	3/11	73.6	− 7.3	−35.5	42.0		+12	100.0	115/75	70	93	3.4	4872	Normal
	3/12												5037	
	3/13	72.7	− 8.1	−50.7			+37	100.0	115/75	49	89	2.3	5714	Normal
	3/16	72.0	− 4.7	−64.8	39.0	5340	+ 1	98.6	110/75	65	85	2.9	0	Normal
A. L.	6/2	65.2	− 0.7	− 0.7	46.0	6345		98.0					0	
56 years, male,	6/9												5485	
chole-	6/10	63.4	− 1.4	+ 4.2	49.0	5955		98.8	105/65	65	60	2.2	5419	Normal
cystectomy,	6/11												5404	
6/20	6/12												5475	
	6/13	63.1	− 2.9	− 9.0	46.0			98.0	100/65	56	63	2.0	0	Normal
	6/16	64.5	− 1.5	−11.5				98.2	95/60	52	55	1.6	0	Normal
	6/18	63.6	− 2.6	−15.9	43.0	6200		97.8	95/60	56	53	1.6	0	Normal
	6/20	63.5	− 2.4	−19.8	43.0			98.4	85/60	49	59	1.6	5338	Normal
	6/21	63.7	− 3.7	−23.5	45.0			100.0	110/70	83	74	3.5	5472	Normal
	6/22	63.4	− 6.5	−30.0	43.0			99.2	110/70	59	74	2.4	5500	Normal
	6/23												5454	
	6/24	61.4	− 4.2	−39.3				100.0	110/70	53	72	2.1	0	Normal
	6/27	61.0	− 2.9	−42.6	39.0			98.6	100/60	56	61	2.0	0	Normal
E. F.	1/7	43.7	+ 1.3	+ 1.3	43			98.0					0	
30 years,	1/13												210	
female,	1/14												3087	
chole-	1/15	43.7	− 1.8	+ 3.6	47		−12	98.0	95/60	69	70	3.6	3073	Slight bowing of the JK segment
cystectomy,	1/16												3078	
1/25	1/17	43.9	− 3.9	− 2.9	42	3190	−13	98.2	95/50	49	66	2.4	3064	Slight bowing of the JK segment
	1/19	44.2	+ 1.7	− 3.7			−16	98.6	95/50	70	69	3.5	0	Slight bowing of the JK segment
	1/22	44.2	+ 1.0	+ 0.9	42			98.4	90/55	72	63	3.4	0	Slight bowing of the JK segment
	1/25	43.9	0.0	+ 3.0	43		− 8	98.4	100/50	97	79	5.6	4450	Slight bowing of the JK segment
	1/26	44.6	+ 2.6	+ 5.6	42		+10	101.0	100/65	116	97	8.3	3775	Normal
	1/27	42.7	− 5.2	+ 0.6	42	3245	+ 8	99.8	110/65	101	80	6.0	3936	Slight bowing of the JK segment
	1/29	43.2	− 2.9	− 6.7	40			99.2	100/55	80	84	5.1	0	Slight bowing of the JK segment
	2/1	43.9	− 0.7	− 8.7			− 8	98.0	95/60	73	72	3.9	0	Slight bowing of the JK segment

P. S. 54 years, female, chole- cystectomy, 12/29	12/15	42.8	+ 3.9	+ 3.9	43			98.0					0	
	12/18	43.0	+ 3.4	+10.8	41	2865	+23	98.0	110/75	40	67	1.9	0	Normal
	12/21	44.0	+ 2.3	+17.9	42		− 7	98.0	95/80	40	65	1.9	0	Normal
	12/23	43.6	+ 1.8	+22.0	39		+19	98.2	110/75	46	64	2.1	0	Normal
	12/26												4987	
	12/27												5020	
	12/28												5031	
	12/29												5031	
	12/30	44.3	+ 1.5	+33.0	36		+105	101.8	115/65	45	82	2.7	5028	Normal
	12/31	44.3	+ 0.5	+33.5	34		+ 7	100.0	120/75	51	83	3.0	5511	Normal
	1/1												5012	
	1/2	43.8	− 1.1	+31.9	38	3510	+51	101.0	115/70	46	83	2.8	5008	Normal
	1/5	44.0	− 2.3	+26.6	38		+ 3	99.0	110/70	48	78	2.7	0	Normal
C. Q. 56 years, female, chole- cystectomy, 1/24	1/6	54.2	+ 1.1	+ 1.1	46			98.0					0	
	1/13												3002	
	1/14												3028	
	1/15	54.1	− 0.5	+ 5.7	48		− 3	99.0	115/70	42	74	2.1	3021	Normal but small
	1/16												3051	
	1/18	54.0	+ 2.3	+ 4.9	44		+ 2	99.0	110/70	41	66	1.9	0	Normal but small
	1/19	54.1	+ 2.2	+ 7.1				99.2	120/70	41	64	1.9	0	Normal but small
	1/22	54.1	+ 0.5	+ 7.5	46			98.0	110/65	41	62	1.8	0	Normal but small
	1/24	54.0	+ 0.4	+ 8.3	44		−19	98.4	100/60	45	70	2.2	3759	Normal but small
	1/25	53.7	− 1.2	+ 7.1	48		+22	100.4	120/65	59	98	4.0	3475	Normal but small
	1/26	53.1	− 5.1	+ 2.0	42	3595	+ 7	100.6	125/75	53	87	3.3	3463	Normal but small
	1/27												3426	
	1/28	53.9	− 2.9	− 5.2	41	3640	+12	100.0	110/60	56	82	3.2	0	Normal but small
	1/31	53.8	+ 0.3	− 4.4	43		0	99.8	110/60	37	72	1.8	0	Normal but small

HTC = hematocrit
TBV = total blood volume
BMR = basal metabolism rate
BP = blood pressure
SV = stroke volume
HR = heart rate
CI = cardiac index

The systolic blood pressure and, to a lesser extent, the diastolic pressure showed a moderate rise above the control values. This rise, which was maximal on the first and second postoperative days, was greater for Groups 2 and 3 than for Group 1. The blood pressures of Group 1 returned to preoperative levels by the fourth day and in Groups 2 and 3 almost to these levels by the seventh day.

The heart rate and stroke volume showed the greatest rise above control levels on the first day, returning toward normal during the seven-day period. In this respect as well, Group 1 showed the most rapid recovery. In all patients the cardiac index was above the control levels on the first day after operation and decreased rapidly toward the base line on the following days. Again in Group 1, the average value returned to the base line by the fourth day, whereas in Groups 2 and 3 the return was less complete by the seventh day.

The basal metabolic rate of seven patients in whom it was measured was usually elevated above the control values on the first day postoperatively, but it did not show a regular nor consistent pattern of return to the control level on the following days as did the other quantities. Therefore, other than the rise on the first postoperative day, there was no significant correlation between the basal metabolism and the cardiac index.

Fluid intake by mouth or vein was considered adequate and at no time were any of the patients dehydrated. The daily parenteral intake of water is recorded in the tables.

Changes in cardiac index showed no consistent relationship with the parenteral fluid intake. In Group 3 during the preoperative period only one patient (A. L.) of the four so tested showed any significant decrease in cardiac index when the parenteral fluids were discontinued.

The postoperative study in Groups 2 and 3 suggests an association between high cardiac index and parenteral fluid intake. However, the exceptions (J. B., W. H., and A. L.) prevent too positive a conclusion in this regard.

Blood volumes were determined both pre- and postoperatively on five patients (C. S., F. S., W. H., E. F., and P. S.). Patient F. S. showed a decrease of 12 per cent, patient P. S. an increase of 23 per cent, while the others showed no significant change.

Except for a slightly positive sodium balance in the immediate postoperative periods, all patients were otherwise in equilibrium as regards the sodium, potassium, chloride, and phosphate ions.

Considering the whole group of patients, there is no definite correlation between the cardiac index and positive or negative nitrogen balance. If, however, the patients are grouped according to sex, it will be noted that the three female patients were all in positive nitrogen balance, and of these patients the one with the greatest positive nitrogen balance had the least increase in cardiac index after operation. The male patients, all of whom were in negative nitrogen balance, showed a similar pattern: the patients with the least negative balance having smaller increases in cardiac index following operation. No conclusions are drawn from the difference with sex because of the small number of patients.

DISCUSSION

No postoperative complications developed in any of the patients studied. The observations recorded, therefore, may be presumed to reflect the effect of anesthesia, operation, and postoperative therapy. It is interesting that the grouping of the patients according to the type of operation also grouped them according to the magnitude of the physiological responses. Subtotal gastrectomy is considered a more major procedure than cholecystectomy because of the greater incidence of complications and, in many clinics, a higher operative mortality. However, in this study the patients undergoing cholecystectomy showed not only greater physiological responses, but also a more difficult convalescence.

The increase in cardiac index following a major operation is of considerable magnitude; however, no certain relationship between the increase in cardiac output and the administration of parenteral fluids is apparent. The observations in this study indicate that the increase in cardiac index on the first and second days following operation is related to the severity of the operation and not solely to the administration of parenteral fluids as suggested by the work of Starr and Mayock.

CONCLUSIONS

1. The increase in cardiac index after operation depends upon the severity of the surgical procedure.
2. This increase in cardiac index is maximal on the first postoperative day and, in general, decreases to preoperative levels by the fourth to seventh day.
3. The postoperative rise in cardiac index is not solely due to the administration of intravenous fluids.
4. There is no absolute correlation between the increase in cardiac index following operation and the level of the nitrogen balance.

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A STUDY OF THE VALUE OF THE ROENTGENOLOGIC DEMONSTRATION OF VALVULAR CALCIFICATIONS

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THE diagnosis of valvular heart disease is at times difficult. This is especially true of aortic stenosis. Kumpe and Bean,[4] in a series of 107 autopsied patients with calcific aortic stenosis, found that this diagnosis had been made clinically in only twenty-three. These authors estimated that in only one-fifth of the patients with aortic stenosis are the textbook criteria fulfilled. In the presence of congestive failure or shock, characteristic murmurs and thrills are frequently absent.

In mitral stenosis the diagnosis is also frequently difficult. This is especially true when the patient is fibrillating with a rapid ventricular rate. In both aortic and mitral stenosis the character of the murmur may be changed by pulmonary or pleural disease.

In many medical centers the roentgenologic search for calcified valves is a routine part of the clinical study of valvular heart disease. Sosman and Wosika[8] demonstrated the diagnostic value of this procedure. As early as 1923, Cutler and Sosman[3] first recorded valvular calcification, which they were able to see fluoroscopically. Christian[2] referred patients to the x-ray department and requested that calcification in the aortic valves be demonstrated. In most instances this was possible.

Valvular calcifications were looked for in every patient admitted to this hospital with heart disease. An effort was made to evaluate the diagnostic and prognostic significance of the finding of these calcifications. Our study was begun in April, 1946, and included all patients with rheumatic valvular heart disease admitted to this 350-bed general hospital up to December, 1949. Seventy-five male patients were included in this study. The youngest patient was 21 years old and the oldest 71 years old. The average age in the series was 50.2 years. The relatively advanced age in the series is to be expected, since the study was conducted at a Veterans Administration hospital where only adults are admitted. The advanced age of our group naturally accounts for a selected type of disease. In this series there were fifty patients with a diagnosis of rheumatic mitral valvular disease and forty-eight with one of rheumatic aortic valvular disease. In twenty-three there was a diagnosis of combined aortic and mitral valvular disease.

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The roentgenologic technique was patterned after that of Sosman.[7] After fluoroscopic examination and localization of the calcification, roentgenograms were taken with a 200 Ma. roentgen tube and a Potter-Bucky diaphragm. The time of exposure varied from one-twentieth to one-tenth of a second. More recently, we occasionally use our spot-filming apparatus which has a 100 Ma. undertable tube and a stationary grid. This is quite satisfactory if the patient is thin enough and the heart small enough so that an exposure of a tenth of a second is adequate. We have seen films of mitral valve calcifications taken by a rotating anode undertable tube with a reciprocating Bucky and Hodges Morgan timer. These films were excellent. While we have had no personal experience with this method, we feel that it is probably the easiest one for demonstrating these calcifications roentgenographically.

In this series calcifications in the aortic valves were found in twenty-one patients, in the mitral valves in fifteen, and in both valves in three. In one instance calcification of the mitral annulus was demonstrated, but the patient is not included in this study. The calcification in this patient was J-shaped and, though nodular, was fairly uniform and bandlike. The patient had no evidence of heart disease. In one patient with calcific aortic stenosis and no evidence of mitral disease, calcification of the mitral annulus was also seen.

The findings in thirty-nine patients with valvular calcifications are summarized in Table I.

In 1939, by roentgen study, Sosman found calcification in the aortic valve in fifty-nine patients, in the mitral valve in fifty-six, and in the mitral annulus in twenty-seven. In our series of seventy-four patients with rheumatic heart disease, calcification was found roentgenologically in the aortic valve in twenty-one, in the mitral valve in fifteen, and in both mitral and aortic valves in three. In the period of study post-mortem examinations disclosed five cases of aortic valve calcification which had not been found roentgenologically. Of these five, only three had been fluoroscoped. In two of these the examination was made unsatisfactory by the presence of pulmonary disease (in one there was a lung tumor and in the other a large pleural effusion). In this period six other patients died of rheumatic heart disease and had post-mortem examinations. Roentgenologic study of these patients did not show any valvular calcifications, and none were found post mortem.

The clinical pattern of our patients with calcific aortic stenosis was similar to that described by Willius[9] and Berk and Dinnerstein.[1] In their studies and ours, the patients with slight or no cardiac enlargement had but few symptoms. They, too, found no correlation between the degree of calcification and the severity of the symptoms.

Their patients had no characteristic electrocardiographic findings. The electrocardiographic findings in our patients were also not characteristic. Those patients with aortic stenosis who had auricular fibrillation had associated mitral stenosis.

All but three patients with mitral valve calcification were admitted for congestive failure. Two-thirds of them had auricular fibrillation. Two patients had electrocardiographic evidence of having had fibrillation for over ten years.

TABLE I.

LOCATION OF CALCIFICATION	NUMBER OF PATIENTS	AVERAGE AGE (YEARS)	HISTORY OF RHEUMATIC FEVER	SYMPTOMS	PHYSICAL FINDINGS	ROENTGENOLOGIC FINDINGS	ELECTROCARDIOGRAM	NUMBER OF POST-MORTEM EXAMINATIONS*
Aortic valves	21	54	8	In patients with normal silhouettes, 4 had no cardiovascular symptoms; in patients with enlarged hearts, all but 1 had symptoms; congestive failure was present in 9, anginal syndrome in 6, vertigo in 2, recurrent syncopal attacks in 1.	Basal systolic murmurs and thrills were heard in 11; 5 of these also had signs of mitral disease. Systolic and diastolic basal murmurs were heard in 7; of these, signs of aortic insufficiency predominated in 3. The blood Wassermann was negative in 6 of these 7 patients; systolic basal murmurs were heard but considered insignificant in 3; no murmur was heard in 1.	Nine heart silhouettes were normal; 12 were enlarged. Calcified valves were seen fluoroscopically in all patients and shown on the films of 19 patients.	Seven patients had normal tracings; 8 had a left hypertrophy pattern; 3 had auricular fibrillation.	5
Mitral valves	15	47	10	Congestive failure was present in 12, impaired effort tolerance in 3.	A diastolic murmur was present at the apex in 13; no murmur was heard in 2.	All patients had mitral silhouettes with enlargement of the left auricle. All calcifications were seen fluoroscopically; 13 were demonstrated on films. In 8 patients the calcifications were seen on 6-foot chest films.	Ten showed auricular fibrillation.	5
Mitral and aortic valves	3	55	1	All patients were in congestive failure.	All had signs of aortic and mitral lesions.	In 1 patient, both calcifications were seen fluoroscopically and on films. In 1 patient the mitral calcification was seen fluoroscopically and on films, but the aortic calcification was seen only on the films.	All three showed auricular fibrillation.	1

*In each of these 11 autopsied cases the roentgenologic diagnosis of valvular calcification was confirmed.

In these patients with mitral valve calcification, as opposed to those with aortic valve calcification, there was a definite correlation between the demonstration of calcification and the severity of the disease. The length of survival, after discovery of calcification, was short. Few patients survived more than a year.

CASE REPORTS

The following examples illustrate the value of the roentgenologic demonstration of valvular calcifications.

CASE 1.—O. H., 53 years old, was admitted to the hospital on June 28, 1947, for congestive failure. He had had acute rheumatic fever at 16 years. For eight years he had had dyspnea on exertion and for four years dyspnea at rest. He had had frequent small episodes of hemoptysis for two months.

Physical Examination.—This revealed an acutely ill, dyspneic man with marked engorgement of the neck veins. There were signs of fluid at both lung bases. The heart was enlarged. The apical rate was 160, and the rhythm was irregular. The first sound was loud. A harsh systolic murmur was heard at the apex. No diastolic murmur could be elicited. The liver was palpated 4 fingerbreadths below the costal margin.

Roentgen Study.—Roentgenograms of the chest showed a very large mitral heart. Fluoroscopy and films showed a calcified mitral valve and an enlarged left auricle. The patient was placed on a cardiac regime and improved. After the ventricular rate was slowed by digitalis, a diastolic rumble was heard at the apex.

Comment.—The roentgenologic demonstration of calcification of the mitral valve established the diagnosis of mitral stenosis in this patient. Because of auricular fibrillation with a rapid ventricular rate, he did not have a characteristic apical diastolic murmur.

CASE 2.—F. McH., 52 years old, was admitted to the hospital on June 22, 1947, for congestive failure. He had had chorea in childhood, and for a period of eight years following this he had had repeated spontaneous epistaxis. He had been treated by a private physician for congestive failure for one month.

Physical Examination.—The patient was dyspneic and orthopneic. The blood pressure was 148/94 mm. Hg. There was a Grade 1 aortic systolic murmur and a diastolic murmur along the left sternal border. There was a to-and-fro apical murmur which was thought to be due to mitral involvement.

Roentgenologic Study.—Mitral and aortic calcifications were found fluoroscopically and on films.

The patient was discharged on July 4, 1947, and was readmitted on Nov. 11, 1948, because of hemptyses of two weeks' duration accompanied by an acute pain in the right chest. There was no change in the physical examination except for signs of consolidation in the left upper lobe. There was a positive Homans' sign on the right. The patient was given anticoagulant therapy but became progressively worse and died on Nov. 11, 1948.

Post-mortem Findings.—The heart was greatly enlarged and calcifications were present in the mitral and aortic valves. Infarcts were present in both lungs.

Comment.—In this patient the physical signs of aortic stenosis were minimal, and those of aortic insufficiency were more prominent. Berk and Dinnerstein,[1] in 1938, stated that in aortic stenosis the classical physical signs may not be present and those of aortic insufficiency may be more prominent. They reported four autopsied patients with aortic stenosis who had clinical signs of aortic insufficiency. In five other living patients with similar findings, x-ray study revealed calcification of the aortic valve.

CASE 3.—R. J., 65 years old, was admitted to the hospital on Sept. 14, 1948, for abdominal pain of ten years' duration.

Physical Examination.—The chest was barrel-shaped and showed physical signs of emphysema. There was a Grade 1 systolic aortic murmur which was considered insignificant clinically.

Roentgen Study.—A chest film showed pulmonary emphysema. During a gastrointestinal series, calcification of the aortic valve was seen fluoroscopically and demonstrated on films (Fig. 1).

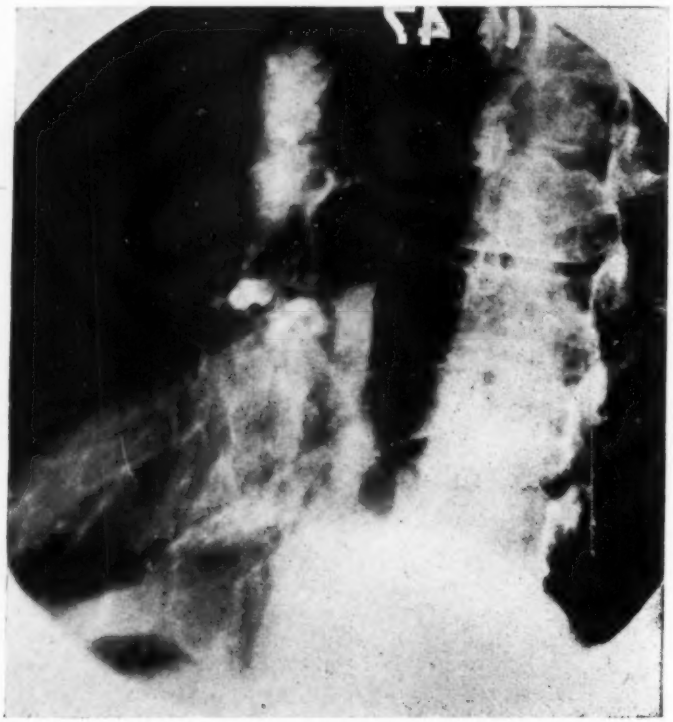

Fig. 1.—Left anterior oblique Bucky film showing calcification of the aortic valve.

Comment.—The diagnosis of calcific aortic stenosis in this patient was made because calcifications were found during a routine gastrointestinal series. The diagnosis had not even been suspected clinically because the character of the murmur was changed by pulmonary emphysema.

The symptoms were minimal, although the deposits of calcium in the aortic valve were quite heavy; this illustrates the well-known lack of correlation between the severity of symptoms and the extent of calcification in calcific aortic stenosis.

CASE 4.—J. H., 68 years old, was admitted to the hospital on April 24, 1947, complaining of shortness of breath. From September, 1944, to the date of admission he was treated by the family physician for paroxysmal bouts of tachycardia, dyspnea, precordial distress, and cyanosis. On the day of admission a bout of tachycardia was accompanied by loss of consciousness.

Physical Examination.—The patient was dyspneic. The pulse rate was 160 and the apical rate 190. The blood pressure was 180/100 mm. Hg. Coarse râles were present in both lungs. The heart sounds were distant, and no murmurs could be heard. The liver was palpable 5 cm. below the costal margin. The electrocardiogram revealed auricular fibrillation with a ventricular

rate of 160. After treatment the patient improved, and a fluoroscopic and roentgenographic study showed calcification of the aortic valve.

Laboratory Studies.—The blood Wassermann and the Kahn tests were strongly positive; the spinal fluid Wassermann test was negative.

The patient improved on cardiac management. At the time of discharge on May 28, 1947, the physical examination revealed signs of aortic stenosis and insufficiency. On Nov. 6, 1947, he was readmitted with symptoms of intestinal obstruction. He was explored, and a carcinoma of the rectosigmoid with metastases to the liver was found. The patient died on Nov. 24, 1947.

Post-mortem examination confirmed the operative findings. There was calcific aortic stenosis with no evidence of syphilitic involvement of the aorta.

Comment.—On admission the patient was in congestive failure, and no murmurs were heard. A roentgenologic study established the diagnosis of calcific aortic stenosis. After improvement, the predominant findings were those of aortic insufficiency. The presence of a strongly positive blood Wassermann in a patient with such findings would ordinarily make one suspect a syphilitic etiology, but the presence of calcification in the aortic valve excluded this possibility.[1]

CASE 5.—D. C., 30 years old, was admitted to the hospital for recurrent, severe hemoptysis and dyspnea. He had had rheumatic fever in 1935. In 1939, he was discharged from the Army because of valvular heart disease. Following his discharge, the patient was incapacitated by frequent, recurrent, severe pulmonary hemorrhages.

Physical Examination.—The patient was moderately pale, dyspneic, and orthopneic. The blood pressure was 122/84 mm. Hg. The pulse rate was 114. There were diminished breath sounds over the right lung posteriorly. There were loud systolic and diastolic murmurs at the apex.

Roentgenologic studies revealed an enlarged mitral heart; fluoroscopically, no calcifications were seen. The electrocardiogram revealed wide abnormal P waves and right axis deviation.

The patient was readmitted for three similar episodes, but during the fourth hospitalization the hemorrhages continued, and he developed Cheyne-Stokes respirations and died on Feb. 5, 1947. During the last hospitalization, calcifications of the mitral valves were seen fluoroscopically and on films (Fig. 2). The electrocardiogram showed auricular fibrillation.

Post-mortem Findings.—There was marked calcification of the mitral valve (Fig. 2), a rheumatic lesion of the aortic valves without calcification, and large dilated bronchial veins along the trachea and the major bronchi.

Comment.—In this patient repeated fluoroscopic examinations were required to demonstrate valvular calcifications. The severe episodes of hemoptysis are explained by the rupture of the dilated bronchial veins. These veins resulted from the severe pulmonary hypertension and served as collaterals between the lesser and systemic circulation.

CASE 6.—V. R., 25 years old, was admitted to the hospital on July 20, 1948, for dyspnea and hemoptysis. There was a history of rheumatic fever at the age of 6 years. In 1944, he was discharged from the Army because of heart failure. For three years prior to admission, he had had recurrent hemoptysis, and for three months he had noted increasing dyspnea.

Physical Examination.—The patient was markedly dyspneic. The blood pressure was 110/80 mm. Hg, the pulse rate 76, the rhythm regular. There were a to-and-fro murmur and a diastolic thrill at the apex. A diastolic murmur was present at the left sternal border.

Roentgenologic Study.—Roentgenograms of the chest revealed a mitral heart. The fluoroscopic examination revealed calcification of the mitral valve. A repeat posteroanterior chest film showed calcification of the mitral valve (Fig. 3). The patient responded well to treatment and was discharged on Aug. 13, 1948. He was readmitted on Sept. 21, 1949, for pain in the right chest and hemoptysis. The diagnosis of pulmonary infarction was made, and the patient was placed on anticoagulant therapy. He developed auricular fibrillation on Oct. 7, 1949, and was digitalized.

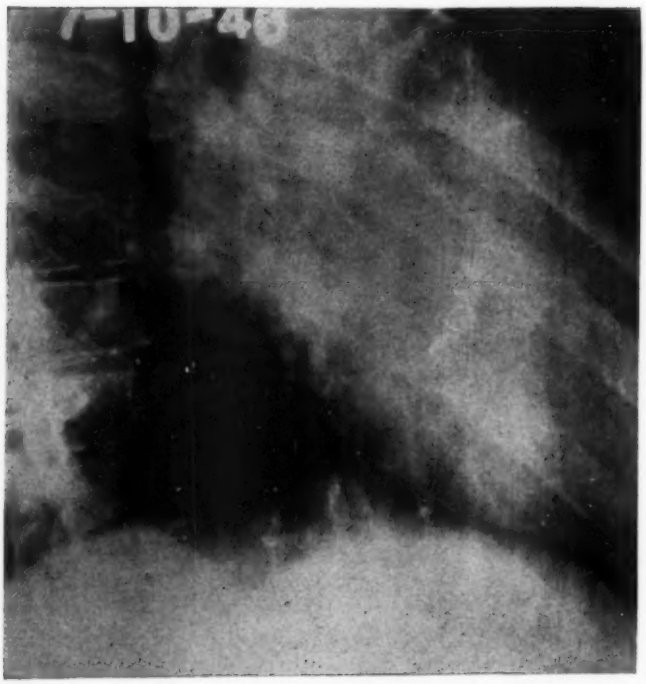

Fig. 2.—A right anterior oblique Bucky film showing calcification in the mitral valve (retouched).

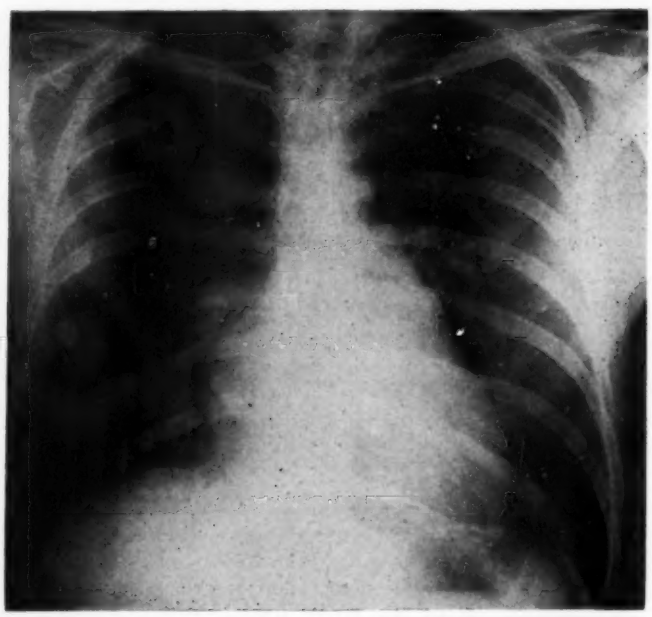

Fig. 3.—Routine chest film showing mitral heart with mitral valve calcification (retouched).

On the same day, he complained of severe pain in the right lower extremity with signs of occlusion of the popliteal artery. Surgical exploration failed to reveal an embolus in that vessel. The patient then became progressively worse and died on Oct. 16, 1949.

Post-mortem examination revealed calcification of the mitral valve. There was a minimal rheumatic lesion of the aortic valve without calcification. An embolus was found in the right deep femoral artery.

Comment.—In this patient it was possible to demonstrate the mitral valve calcifications on a six-foot posteroanterior chest film. In seven other patients we were able to show the calcifications on the routine chest film.

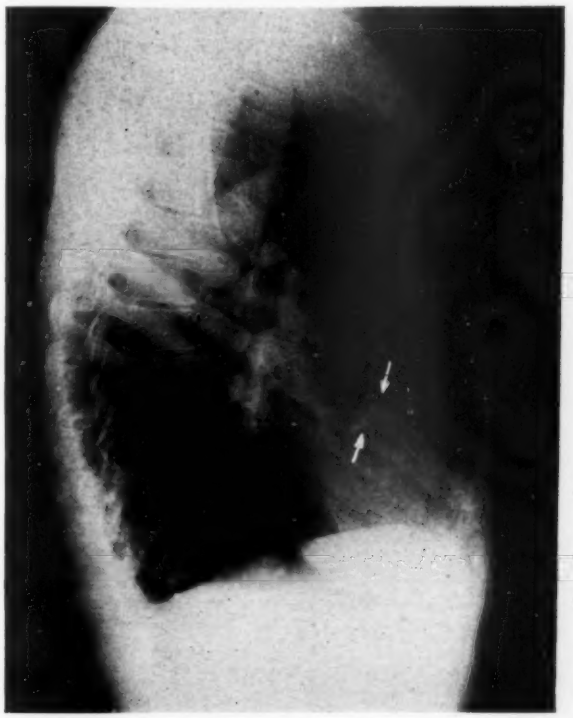

Fig. 4.—Lateral six-foot film showing calcification of the aortic valve.

CASE 7.—C. L., 65 years old, was admitted to the hospital on Aug. 15, 1949, for nausea, vomiting, and abdominal pain. He had been treated for rheumatic heart disease with failure for six years.

Physical Examination.—The blood pressure was 130/70 mm. Hg. There were a systolic thrill and murmur at the aortic area and a diastolic murmur at the left sternal border which was transmitted to the apex.

Roentgenologic Study.—A posteroanterior chest film was negative. Fluoroscopic study revealed a calcified aortic valve (Fig. 4).

Comment.—In this patient a routine chest film was negative, although aortic calcifications were demonstrated fluoroscopically. Almost one-half of our patients with calcific aortic stenosis had normal silhouettes. This patient is somewhat an exception in that, despite a normal silhouette, he had symptoms of congestive failure.

CASE 8.—J. W., 56 years old, was admitted to the hospital on April 25, 1946, for shortness of breath and substernal pain of one year's duration. The patient had been digitalized by his physician because of swelling of the ankles and paroxysmal nocturnal dyspnea.

Physical Examination.—The patient was dyspneic and orthopneic. The blood pressure was 160/90 mm. Hg, the pulse rate 120 and of a bigeminal type. There were fine râles at both bases. There was a Grade 1 systolic murmur at the apex. The liver was enlarged, and there was edema of the legs. An electrocardiogram showed a pulsus bigeminus due to nodal premature contractions.

Roentgenologic Study.—Chest films showed enlargement of the left ventricle.

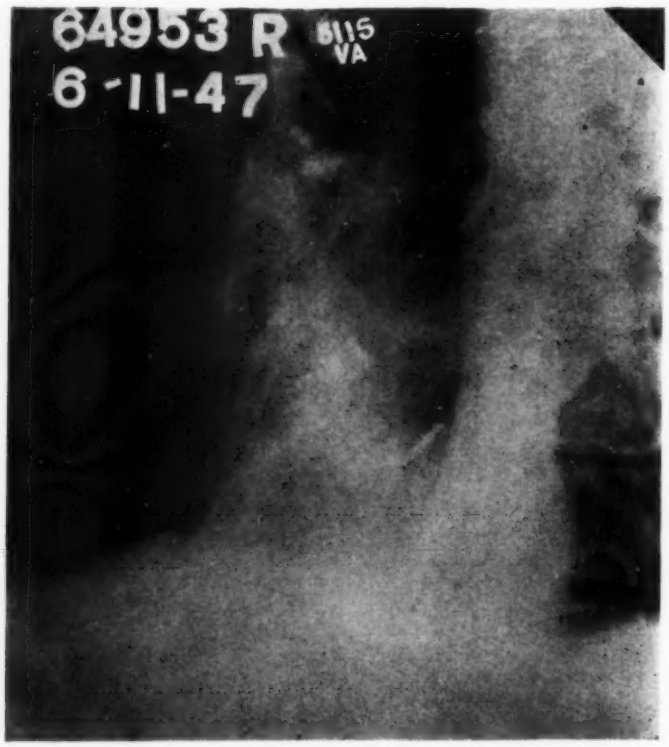

Fig. 5.—Left anterior oblique film showing aortic calcification (the mid-silhouette and mitral calcification below and posterior).

The patient responded to treatment and was discharged on July 31, 1946, with the diagnosis of hypertensive heart disease and congestive failure. He was readmitted on April 27, 1947, for recurrent congestive failure. Physical examination was essentially the same as on the previous admission. On May 11, 1947, he complained of acute pain in the left side of the chest followed by hemoptysis. On Dicumarol therapy the patient improved. Fluoroscopy at this time revealed calcification of the aortic valve. A chest film showed multiple pulmonary infarcts with a small left pleural effusion. On May 20, 1947, the patient suddenly became quite dyspneic and died.

Post-mortem examination revealed calcific aortic stenosis with a mild degree of mitral stenosis without calcification. There were three large pulmonary infarcts.

Comment.—In this patient, who was in congestive failure, the diagnosis of hypertensive heart disease was made. As mentioned by Kumpe and Bean,[4] the so-called classical physical signs of aortic stenosis are obscured by congestive failure. In our patient, even after compensation had been restored, there were no physical signs of aortic stenosis.

CASE 9.—R. T., 53 years old, was admitted to the hospital on April 8, 1947, for ascites and edema. He had been treated for rheumatic heart disease since 1932. He had had recurrent swelling of the legs and abdomen since 1946.

Physical Examination.—The patient was dyspneic and cyanotic, and the neck veins were engorged. The blood pressure was 125/85 mm. Hg. The scleras had a subicteric tint. Diminished breath sounds were heard at the right base and fine râles at both bases. The cardiac rhythm was totally irregular with an apical rate of 120 and a radial rate of 80. To-and-fro apical and aortic murmurs were present. Marked ascites and marked edema of the legs and scrotum were present.

Roentgenologic Study.—Chest films showed a mitral heart with an infiltration at the base of the left lung and a little fluid at the left costophrenic angle; the latter findings were considered to be due to a pulmonary infarct. Fluoroscopy and special films revealed calcification of the aortic and mitral valves and enlargement of the left auricle (Fig. 5). In spite of treatment, the patient did poorly and on May 7, 1947, developed bilateral phlebothrombosis and was placed on Dicumarol therapy. After six months hospitalization, the patient was discharged at his own request. A follow-up letter stated that he had died two months after discharge from the hospital.

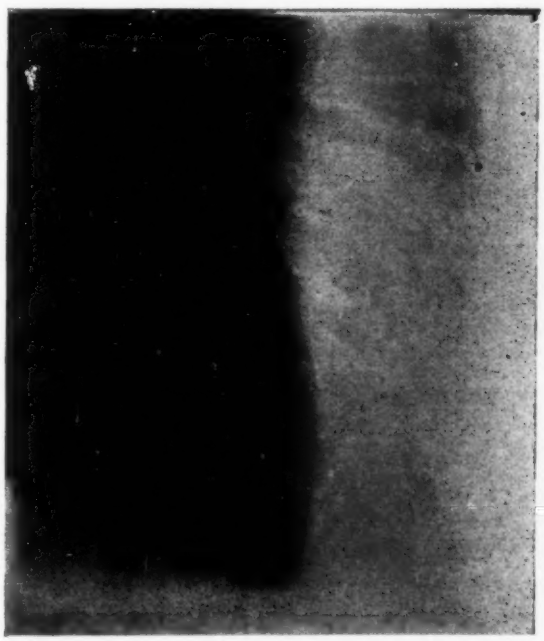

Fig. 6.—Posteroanterior film taken with spot-filming apparatus and stationary grid showing calcification of the mitral annulus.

Comment.—This is an example to illustrate calcification of both aortic and mitral valves. Clinically, the cyanosis, subicteric tint, ascites, and marked jugular distention suggested tricuspid disease, even though deep systolic pulsations of the jugular vein were not noted.

CASE 10.—G. R. (not included in this series), a woman, 76 years old, had no symptoms referable to the cardiovascular system. Calcification of the mitral annulus was seen on routine gastrointestinal series (Fig. 6).

Comment.—There was a very low incidence of annulus calcification in this series. We feel it is largely explained by the higher incidence of this type of cal-

cification in women. Menezes de Oliveira[5] stated that annulus calcification in women is more frequent because they have a higher proportion of metabolic diseases, especially after the menopause, and because they have a higher incidence of hypertension. We have each seen several cases of annulus calcification at other hospitals, and the case reported is an example seen in private practice.

SUMMARY

In a period of about three years, seventy-four patients with rheumatic valvular heart disease were studied. In practically every patient an effort was made to find valvular calcifications by roentgenologic methods. We have tried to correlate the presence of valvular calcification with the clinical findings and prognosis. In a few instances it was only the finding of these calcifications that made the diagnosis possible. There was no correlation between the presence of calcification in the aortic valve and the severity of the disease. In calcification of the mitral valve, on the other hand, such a correlation was present. Few patients with this condition survived more than a year.

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THE DETECTION OF UNSUSPECTED HEART DISEASE IN PHOTOFLUOROGRAPHIC CHEST SURVEYS

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IN AN attempt to evaluate the photofluorographic tuberculosis mass survey as a means of detecting unknown heart disease, a study was conducted for a period of thirty-one months by the Heart Division of the San Francisco Tuberculosis Association (San Francisco's affiliate of the American Heart Association). During this time, approximately 155,000 35 mm. minifilms were taken in search of tuberculosis, either by the mobile unit or at the central office of the Tuberculosis Association. The tuberculosis survey film readers were instructed to report, in addition to tuberculosis, any suspected abnormality of the cardiovascular shadow. The first 93,000 films were also read independently by one of us (A. S.) especially for abnormality of the cardiac silhouette.

If any film reader suspected heart disease, the subject was invited to return for a fluoroscopic re-examination because of "a questionable finding." Except in the letterhead, "Heart Division of the San Francisco Tuberculosis Association," the letter did not mention the heart as being under suspicion. Of the 1,356 such subjects invited to return, 846 did so and were fluoroscoped by one of us (A. S. or M. B. H.). In 174 cases the fluoroscopist found nothing suspicious; in 158 the findings were questionable. No further action was taken in these two groups except to send our findings to the physician of those patients who requested that a report be sent.

There were 514 cases still suspected of disease of the heart or aorta. Each of these was asked to consult his physician (or if he had no physician, to consult a physician on the referral roster of the San Francisco County Medical Society) or was referred to a clinic. It was explained to the patient that our fluoroscopic impression was not equivalent to a diagnosis of heart disease. A letter was then sent to the physician or clinic stating the abnormality found by fluoroscopy.

Since we were later able to obtain clinical reports on only 193 cases of the 514 referred, we think that a large number of these patients failed to consult their physicians as we had requested. Others were lost for various reasons, such as change of residence, change of physician, and so forth.

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FINDINGS

Table I shows the films marked as "cardiac" by the two readers (per thousand cases). It is to be noted that the two readers agreed only in 170 instances and disagreed in 796, most of the disagreements being attributable to the cardiologist because he read one-half again as many "positives" as did the tuberculosis film reader. From the statistical evidence at hand we were unable to determine whether the cardiologist's level of suspicion was justified.

TABLE I. THE TOTAL NUMBER AND RATE PER 1,000 OF SUSPICIOUS CARDIAC SHADOWS

	NUMBER FILMS READ	SUSPICIOUS CARDIAC SHADOWS REPORTED							
		BY CHEST-READING PANEL		BY CARDIOLOGIST		BY BOTH		TOTAL	
Period of double film reading (May 1, 1946 to Dec. 31, 1947)	93,513	422	4.5	714	7.6	170	1.8	966	10.3
Period of single film reading (Jan. 1 to Dec. 31, 1948)	61,508	390	6.3					390	6.3
Total	155,021	812	5.3	714	7.7	170	1.8	1,356	8.7

TABLE II. THE RESULTS OF FLUOROSCOPIC RE-EXAMINATION OF SUBJECTS WITH SUSPICIOUS CARDIAC SHADOWS

	TOTAL REPORTED	FLUORO-SCOPED		SUSPICION ACCEPTED		QUESTIONABLE FINDING		SUSPICION REJECTED	
Period of double film reading:									
Chest readers' findings	422	271	(64%)	171	(63%)	45	(17%)	55	(20%)
Cardiologist's findings	714	440	(62%)	275	(63%)	97	(22%)	68	(15%)
Concurrent findings by both	170	110	(65%)	94	(86%)	12	(11%)	4	(3%)
Period of single film reading:									
Chest readers' findings	390	245	(63%)	162	(65%)	28	(12%)	55	(23%)
Total series	1,356	846	(62.4%)	514	(60.7%)	158	(18.7%)	174	(20.6%)

Fig. 1 shows the age distribution of all subjects selected by any reader as having a suspicious cardiac shadow. Since the age distribution of the total surveyed population is not known, we are unable to draw any conclusions as to the potential rate of discovery of cardiac disease in various age groups in the

population as a whole. The sex distribution of "suspects" was: 629 males and 727 females.

Table II shows that two-thirds, or 846, of those invited for a fluoroscopic re-examination actually returned for fluoroscopy. In 63 per cent of these, the "positive" film reading was confirmed by fluoroscopy. Since the cardiologist read many more films "positive" than did the tuberculosis film readers, he had many more confirmations to his credit.

In those films read "positive" by both readers concurrently, fluoroscopic confirmation was high, suspects being rejected as normal or borderline in only 3 per cent.

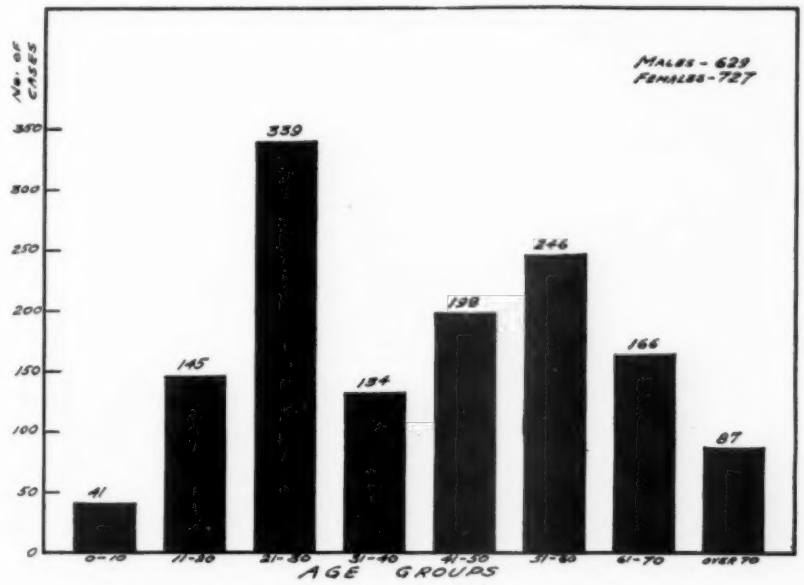

Fig. 1.—Age distribution of 1,356 patients with abnormal cardiovascular shadows in 155,021 35 mm. x-ray films.

In an analysis of the major categories of cardiac abnormalities observed, it is seen that the "positive" film reading was confirmed by fluoroscopy more often in some than others. Table III presents these data. From this it appears that "enlarged left ventricle" and "abnormal aorta" are the most consistent abnormalities found by the film readers which were confirmed by fluoroscopy.

There were re-examinations of ninety children below the age of 18 years. Much poorer fluoroscopic confirmation was found in these, because only 42 per cent of the film diagnoses were accepted by fluoroscopy (two-thirds as many as were accepted in the adult group) and 40 per cent rejected (more than twice as many as were rejected in the adult group).

Reports of a clinical examination were obtained in only 193 (37 per cent) of those persons who were requested to consult their physicians. Reports were received from a number of physicians, each reporting according to his own method without previous indoctrination by us. Table IV summarizes these reports. Note that reports from the Children's Diagnostic Center concern only

cases previously unknown. Unfortunately, due to a misunderstanding, information concerning children with previously known heart disease was not made available for this survey. Because the number of children is small (about 10 per cent of the "suspects") we believe this factor to have little influence on our statistics. The relative incidence of the several cardiac diseases is not very different from the known incidence in the general population, except that congenital heart disease appears to have been found with somewhat greater frequency. The most significant fact emerging from all these clinical reports is that the clinicians confirmed the fluoroscopist's impression in 85.5 per cent of the subjects examined clinically.

TABLE III. THE INCIDENCE OF FLUOROSCOPIC CONFIRMATION OF FILM READERS' DIAGNOSES

FILM READERS' IMPRESSION	TOTAL FLUORO-SCOPED	FLUOROSCOPIC RE-EXAMINATION					
		IMPRESSION ACCEPTED		IMPRESSION HELD QUESTIONABLE		IMPRESSION REJECTED	
"Enlarged heart"	495	287	(58%)	98	(20%)	110	(22%)
"Enlarged left ventricle"	145	106	(73%)	30	(21%)	9	(6%)
"Enlarged conus; prominent pulmonary artery, mitral configuration, etc."	129	66	(51%)	22	(16%)	41	(33%)
Other diagnoses, including "abnormal aorta"	77	55	(72%)	8	(10%)	14	(18%)

From this table it can be seen, however, that only eighty-nine cases of previously unsuspected heart disease were discovered by this survey—a total of 0.059 per cent of the 155,021 films read.

DISCUSSION

From this study of a large series of minifilms it is evident that the chest survey film readers selected from five to eight films per thousand as suspicious of cardiovascular disease, according to the degree to which the reader was heart conscious. A fluoroscopic examination rejected one-third of these. Of those confirmed by fluoroscopy, clinical study rejected about 15 per cent. This last figure is not entirely dependable statistically, however, because we have a report on only a small proportion of the patients (37.5 per cent).

In this series about one-half of those clinically confirmed were apparently previously unsuspected cases of heart disease (Table IV). These cases represent the actual yield of the cardiac survey. Probably due to poor cooperation of the "suspects," there were only eighty-nine previously unknown cases of cardiac disease discovered per 155,021 films, which is a rate of 0.59 per thousand. However, the clinical reports on approximately three-quarters of the patients selected for follow-up were not received. If a complete follow-up had been possible,

it is estimated that approximately four times as many previously unknown cases of heart disease would have been discovered.

TABLE IV. DIAGNOSTIC FOLLOW-UP IN 193 CASES OF SUSPECTED HEART DISEASE. (IN PARENTHESES ARE CASES OF HEART DISEASE PREVIOUSLY UNKNOWN.)

CLINICAL DIAGNOSES	FOLLOW-UP REPORTS FROM							
	PRIVATE PHYSICIAN		CLINICS		CHILDREN'S DIAGNOSTIC CENTER		TOTAL	
Total reports	115		45		33		193	
No evidence of heart disease	10		6		12		28	(14.5%)
Hypertensive cardiovascular disease	16	(9)	15	(6)			31	(15)
Arteriosclerotic or coronary heart disease	23	(4)	6	(2)			29	(6)
Rheumatic heart disease	11	(5)	5	(1)	8	(8)	24	(14)
Congenital heart disease	2	(0)	5	(2)	7	(7)	14	(9)
Unspecified heart disease and other types	53	(36)	8	(3)	6	(6)	67	(45)
Total clinically positive cases	105	(54)	39	(14)	21	(21)	165	(89)

This would still be a very small rate of discovery of unknown heart disease. It is well known that the variability of cardiac size is so great that considerable cardiac enlargement may take place without making the heart appear large enough by x-ray examination to attract attention. Moreover, many forms of serious cardiac disease are not characterized by enlargement of the heart. Finally, if the breath is held for any appreciable time in full inspiration before the film is taken, as frequently happens in a survey conducted primarily for the detection of pulmonary disease, the heart may decrease considerably in size (Valsalva's experiment). Thus, routine films taken in a tuberculosis mass survey are not well suited for determining smaller degrees of cardiac enlargement.

The minifilms studied may be divided into three categories according to the appearance of the cardiovascular shadow: (1) those unequivocally normal, (2) those with gross abnormalities of the cardiovascular shadow, and (3) the borderline group, in which lesser abnormalities are present, together with variations of the normal cardiovascular shadow. The first group includes cardiac disease which is entirely undetectable by radiography. The second group represents gross cardiac disease which is easily detectable by radiography, individually or in mass surveys. The possibility of finding previously unknown cases of cardiac disease in this latter group is not great.

Perhaps the most important group from the standpoint of this type of survey is Group 3, which includes individuals without cardiac disease who have cardiac shadows larger in size than the average and those who have cardiac disease but show only minor changes in size and shape of the cardiac shadow. This group

is likely to contain most cases of asymptomatic cardiac disease and, therefore, most of the previously unknown cases of heart disease toward which the survey was directed.

The use of a fluoroscopic re-examination as a screening procedure in this group appears to be important. In our survey only 60.7 per cent (193) of the "suspects" selected by the readers were still considered as definitely abnormal after fluoroscopy. It is believed that fluoroscopy thus can, at least in part, eliminate the false-positive cases in which the heart appears unduly large on the survey film due to technical factors, such as rotation of the subject, high position of the diaphragm because of failure to take a deep breath, or abdominal constriction because of tight clothing.

The patients considered as being in the "questionable" group after fluoroscopy were not informed of our impression. The decision to follow this conservative policy was reached after most careful consideration. It is well known that a cardiac neurosis may easily be precipitated in a susceptible individual who is suddenly confronted with the prospect of possible heart disease.[1] Undoubtedly some cases of heart disease were thus missed, but in following our conservative policy we felt that these possible omissions were, on the whole, in the best interest of the patient, in contrast with the discovery of possible tuberculosis by this type of survey, where immediate follow-up and examination of the patient are important both from an individual as well as a public health standpoint.

As the result of making a fluoroscopic re-examination before referring the "suspect" for a clinical examination, 400 persons out of every 1,000 cases of suspected cardiac disease will be spared what we feel might be an unnecessary clinical investigation. According to our experience, the fluoroscopic re-examination required about fifteen minutes of a physician's time, as compared with the much greater expenditure of a physician's time which would have been required for a clinical examination of each of these individuals. In addition, these 400 patients would be spared the inconvenience, expense, and possible unfavorable psychological impact of a clinical examination.

It is seen from this survey that the yield of unknown cardiac disease discovered by the routine minifilm survey method, even with the additional aid of fluoroscopy, is relatively small. It can be increased by special studies or by repeated reading by trained cardiologists or roentgenologists, but this would add an estimated 20 per cent to the cost of a chest survey. However, the fact remains that in our survey eighty-nine cases of previously unknown heart disease were discovered. The detection of these eighty-nine cases is of unquestionable importance to the particular individuals concerned. But because of the limitations of roentgenography in the detection of cardiac disease in general, and of the minifilm technique in particular, we feel that a cardiac case-finding survey as a by-product of a tuberculosis survey may not justify itself, particularly without the follow-up aid of fluoroscopy. In addition to the small yield of hitherto unknown cases of heart disease, a large number of individuals with heart disease could slip by the survey undetected. Furthermore, among the surveyed population there could easily develop a false sense of security, in that failure to be discovered as a "cardiac" could well be interpreted in the same sense as a negative report for tuberculosis—an obviously false conclusion.

This discussion is limited to an evaluation of routine minifilm technique as applied to the detection of cardiac disease. Even in the infinitely more suitable application of photofluorography to the detection of tuberculosis, it has been shown[2,3] that there are important limitations, such as serious disagreements between readers or even disagreements between two or more readings by the same individual. In view of such limitations and the results of our survey, the use of the minifilm technique in the detection of cardiac disease appears unreliable.

SUMMARY

1. Minifilms (155,021), taken during a tuberculosis survey, were reviewed for the purpose of detecting previously unknown heart disease. In 1,356 (0.87 per cent) abnormally appearing cardiac shadows were considered to be present.

2. Fluoroscopic re-examination of 846 individuals with abnormally appearing shadows confirmed an abnormality in only 514 cases (60.7 per cent). Thus fluoroscopy is of value in eliminating many false-positive minifilms, especially those due to technical difficulties.

3. Clinical studies by various physicians of 193 of the patients with abnormal findings confirmed fluoroscopically revealed that twenty-eight (14.5 per cent) had no evidence of heart disease. Evidence of clinical heart disease was found in 165 (85.5 per cent); in eighty-nine (46.1 per cent) of these, heart disease was previously unknown.

4. In a survey of 155,021 minifilms, only eighty-nine cases (0.059 per cent) of previously unknown heart disease were discovered.

5. The eighty-nine cases of previously unknown heart disease discovered by the minifilm technique in routine chest surveys, although important in themselves, represent a disappointingly small yield for a survey of this magnitude. While this may be due to two important factors, (1) a conservative policy in an attempt to avoid precipitating cardiac neuroses, which can be a troublesome by-product of such a survey, and (2) lack of patient cooperation, we believe the procedure for detecting unknown heart disease as a by-product of a tuberculosis survey not of sufficient value to warrant its routine use. One of the chief objections of such films for a cardiac survey is the inaccuracy of the films in the estimation of heart size.

We wish to express our gratitude to the minifilm readers' panel, the members, and the technical staff of the Casefinding Committee of the San Francisco Tuberculosis Association for making this survey possible; to Drs. Francis L. Chamberlain and Saul J. Robinson for participating in some phases of the survey; to various physicians and clinics for making clinical information available to us; and to Drs. Charles W. Barnett, L. H. Garland, R R. Newell, and Paul D. White for valuable suggestions in the preparation of the manuscript.

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ANGIOCARDIOGRAPHY IN THE LOCALIZATION OF FOREIGN BODIES IN THE HEART

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WHILE intrathoracic foreign body localization is infrequently required in civilian practice, it is not rare in military practice, particularly in time of war. Harken and associates,[1,2,3] in 1946, reported their experience in removing 134 foreign bodies associated with the heart and great vessels. In addition to these, approximately an equal number of patients was referred to them as having foreign bodies in the heart, but these were found on careful fluoroscopy to have extracardiac fragments. In those patients actually operated upon, one-third, thought originally to have intracardiac fragments, were found to have extracardiac foreign bodies.

Harken and associates also indicated that the exact location of the foreign body within the heart determines whether or not surgical removal is technically possible. Only thirteen of twenty-eight intracardiac fragments could be removed in the patients they operated upon. In their opinion, to be removable, a foreign body must be palpable in the unopened heart and able to be grasped from the outside and held in a fixed position. Then, while the foreign body is so controlled, the heart is incised and the foreign body quickly extracted. Therefore, foreign bodies embedded in the septum are difficult or impossible to remove. It becomes apparent that there is a need for a more accurate means of determining the precise localization of intrathoracic foreign bodies.

We have recently studied four patients with intrathoracic foreign bodies which were thought to be in, or in close proximity to, the heart or aorta. In two cases, angiocardiography showed that the metallic fragments were not within or dangerously close to these structures. In the other two patients angiocardiography showed that the foreign bodies were within the heart. These latter two cases will be presented briefly.

CASE 1.—A 20-year-old soldier was wounded in Korea on July 27, 1950. He was struck by a piece of mortar fragment which entered the right anterior chest, and there was no wound of exit. He was treated conservatively with repeated thoracenteses and was evacuated to the United States, being admitted to Fitzsimons Army Hospital on Oct. 2, 1950.

On admission his only complaint was an occasional, sharp, nonradiating pain which was located just above the left nipple and along the left lower costal margin. The only pertinent physical findings besides a well-healed wound of entrance in the right chest at the anterior axillary line were an accentuated P_2 and the presence of a Grade 2, blowing, apical, systolic murmur.

Posteroanterior and lateral roentgenograms of the chest showed a metallic foreign body which appeared to be within the heart (Figs. 1 and 2).

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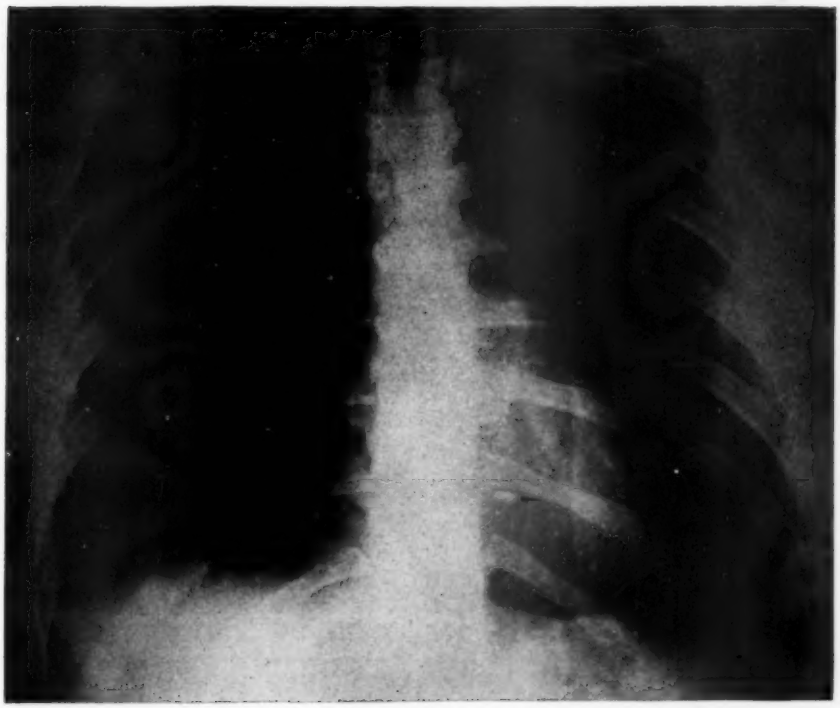

Fig. 1.—A metallic foreign body is revealed which appears to be in the heart (posteroanterior view).

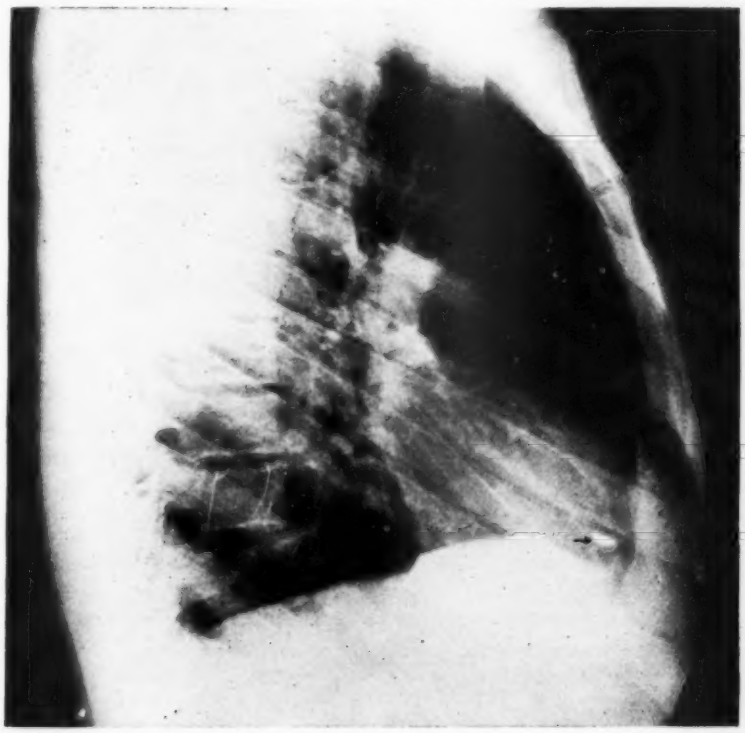

Fig. 2.—Same as Fig. 1 (lateral view).

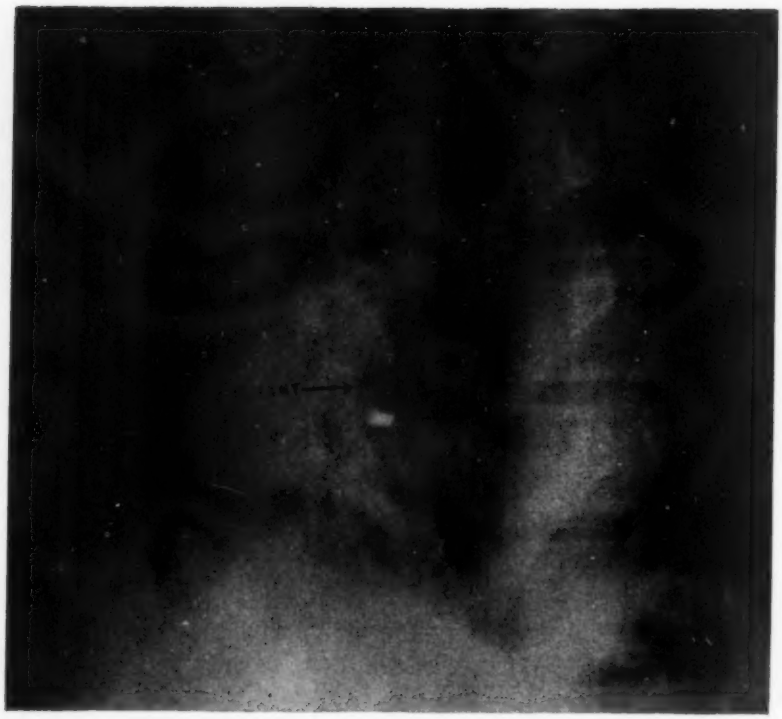

Fig. 3.—This shows the right side of the heart opacified, and the foreign body may be seen to lie slightly to the left of the right ventricular cavity.

Fig. 4.—This shows both ventricular cavities well opacified and the interventricular septum well delineated. The foreign body is seen to lie within the interventricular septum with one end projecting only slightly into the right ventricular cavity.

Fluoroscopy revealed the presence of a foreign body which was thought to be in the region of the right ventricle and which moved synchronously with the heart beat. Electrocardiograms showed evidence of an extensive pericarditis or superficial myocardial injury.

Angiocardiography was performed ten days after admission. Films obtained at that time revealed the foreign body to be embedded in the interventricular septum (Figs. 3, 4, and 5).

As a result of these studies, it was concluded that the foreign body was in the heart, being embedded in the interventricular septum. It was thought that a foreign body in this position would not be accessible to surgical removal. The patient's convalescence was uneventful until October 18 when he developed a pericardial effusion which subsided rapidly without any treatment, and he has remained asymptomatic since. Electrocardiograms gradually returned to normal, and he subsequently has been returned to duty.

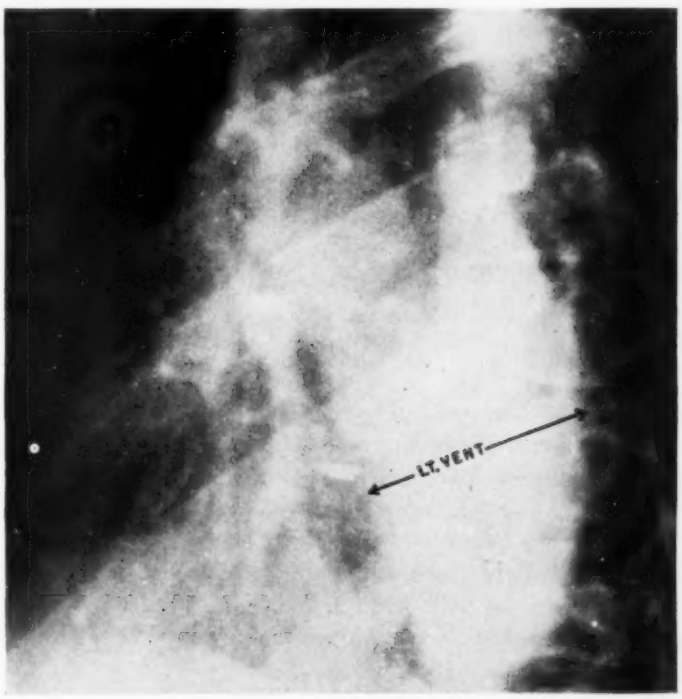

Fig. 5.—This shows the left side of the heart well opacified, and the foreign body is seen to lie just to the right of the left ventricle.

CASE 2.—An 18-year-old soldier was wounded in Korea on Sept. 18, 1950. A fragment of a grenade entered the right chest at the posterior axillary line and made no wound of exit. He had a sucking wound of the chest which was treated in Japan, and he was evacuated to the United States, being admitted to Fitzsimons Army Hospital on Oct. 1, 1950.

On admission he had no complaints referable to the cardiovascular system. Physical examination revealed a well-healed wound of entrance, and examination of the cardiovascular system revealed signs of pericardial effusion. An extremely loud friction rub was audible over the entire precordium, but it was maximal at the second and third intercostal spaces close to the sternum. No murmurs were heard.

Posteroanterior and lateral roentgenograms of the chest showed some enlargement of the cardiac silhouette and a metallic foreign body which appeared to lie within the heart (Figs. 6 and 7).

Cardiac fluoroscopy showed generalized enlargement of the cardiac silhouette, decreased pulsations, and the metallic foreign body, which moved vigorously and synchronously with the heart beat. The electrocardiogram showed a diffuse pericarditis or superficial myocardial injury pattern.

Angiocardiography was done on October 17. Films obtained at that time revealed the foreign body to be within the right ventricular cavity (Figs. 8 and 9).

As a result of these studies, it was felt that the foreign body was definitely localized within the right ventricle and that it probably would be accessible to surgical removal. The presence of a pericardial effusion was further confirmed.

Operation was deferred, pending convalescence from the chest wound. The convalescence was interrupted by a severe attack of homologous serum hepatitis and another pericardial effusion. From time to time, the patient complained of precordial pain and had slight elevations of temperature. During these episodes electrocardiographic evidence of pericarditis or superficial myocardial injury recurred. He did not show clinical or radiographic evidence of pericardial effusion. It is not known whether these episodes represented recurrent attacks of pericarditis or further myocardial injury from the retained metallic fragment.

Operation with removal of the foreign body was successfully performed on Feb. 27, 1951. The fragment was located in the spot where the angiocardiograms had shown it to be. The left end projected slightly deeper into the interventricular septum than the original studies had shown. Possibly it had moved slightly in the three months intervening after angiocardiography. This suggests that contrast studies should be carried out within a few days prior to operation.

COMMENT

Angiocardiography can be easily carried out on patients suspected of having intracardiac foreign bodies as soon as their condition is stabilized. Such studies carry but slight risk and appear to offer valuable information as to the precise location of the foreign body and perhaps in the determination of the feasibility of its surgical removal.

The technique used in producing the pictures is no different from that customarily employed in cardiac angiography. A series of pictures must be made in rapid sequence, usually at 1-second to 1½-second intervals, in order to obtain separate visualization of the various cardiac chambers in relation to the foreign body. While any rapid cassette changer or a suitably adopted roll film camera can be used in producing the pictures, a changer with a fluoroscope located behind the exposure chamber is a great aid in this type of study. This permits more precise positioning than is otherwise possible. A modification of the Schwarzchild type of changer was used.[4,5] The left anterior oblique position was used in cases of intracardiac foreign bodies, but slight changes in the degree of obliquity may be desirable, depending on the apparent location of the fragment fluoroscopically. Foreign bodies associated with the great vessels may best be seen in the posteroanterior view.

While these cases by no means prove the value of this method of study, they indicate that the method is feasible and useful, and further application seems justified.

SUMMARY

1. A new method for localizing radiopaque intrathoracic foreign bodies by angiocardiography is presented.

2. Two cases of intracardiac foreign body are presented in detail, illustrating the use of angiocardiography. In one, removal of the foreign body was thought not technically possible because of its location. In the other, removal was carried out.

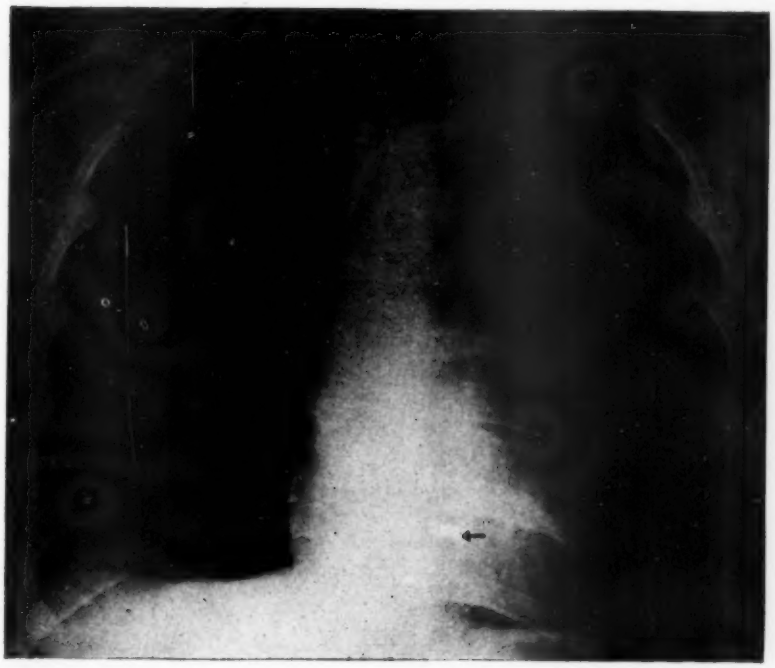

Fig. 6.—This posteroanterior roentgenogram of the chest shows some enlargement of the cardiac silhouette and a metallic foreign body which appeared to lie within the heart.

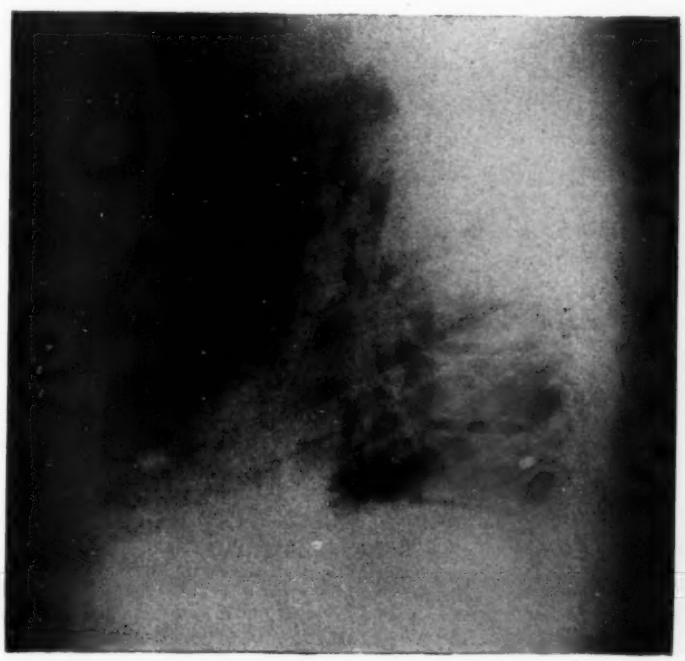

Fig. 7.—Same as Fig. 6 (lateral view).

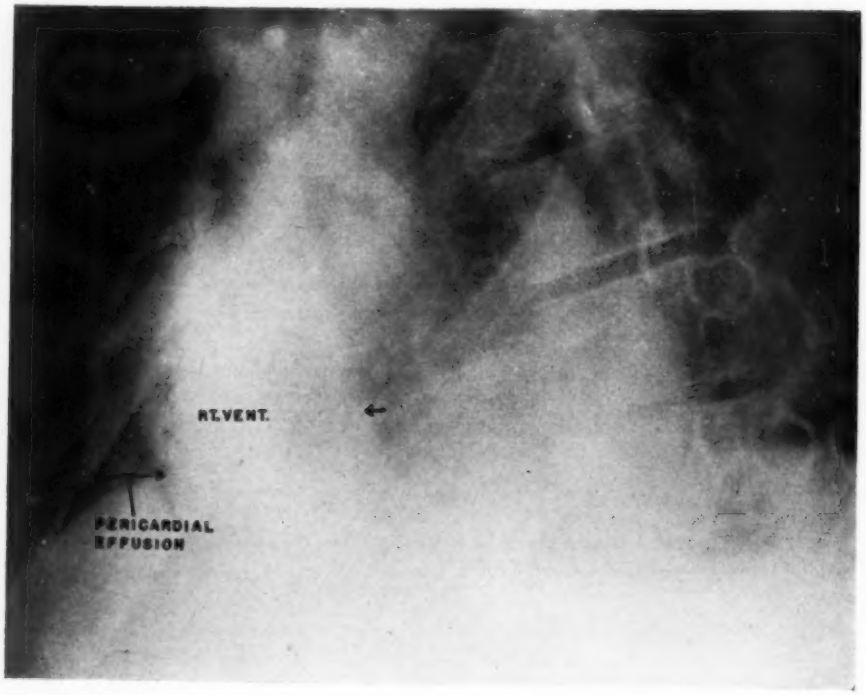

Fig. 8.—This shows the right side of the heart well opacified, and the foreign body is seen within the right ventricle. This picture also demonstrates a pericardial effusion: the right cardiac border lies 2 cm. lateral to the ventricular cavity (4 mm. is the normal thickness of the right ventricular wall).

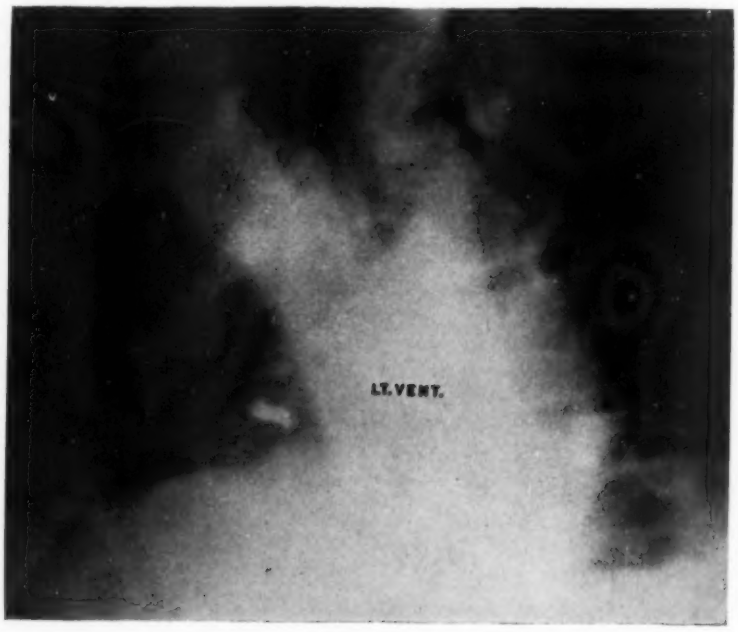

Fig. 9.—This shows the left ventricle well opacified, and the foreign body can be seen well to the right of the cavity. The pericardial effusion is again demonstrated.

3. Our experience suggests that angiocardiography should be performed within a few days of operation, as the foreign bodies may move or become more deeply embedded in the cardiac tissues.

4. While this is a preliminary report, the method appears to offer considerable information at slight risk and to merit further application.

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SPATIAL VECTORCARDIOGRAPHY: RIGHT VENTRICULAR HYPERTROPHY AS SEEN IN CONGENITAL HEART DISEASE. VII.

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THE establishment of the presence of hypertrophy of the wall or increase in the mass of the right ventricle is of fundamental importance in the differential diagnosis of congenital cardiac malformations. Fluoroscopy and electrocardiography, particularly when employing unipolar chest leads,[1,2] are most useful clinical tools for this purpose. Neither, however, is capable of making an unequivocal statement at all times. Cardiac catheterization and angiocardiography are at times necessary to identify hypertrophy or enlargement of the right ventricle. Since these techniques are not entirely without risk, aside from being greatly time consuming, their application as routine clinical procedures is not possible.

In order, possibly, to add more certainty to the diagnosis of right ventricular hypertrophy, a vectorcardiographic analysis was undertaken. Only patients with well-authenticated hypertrophy or enlargement of the right ventricle alone were selected from a large series of patients with congenital heart disease. The diagnoses had been established in the majority by angiocardiography or cardiac catheterizations. There were patients with marked, moderate, and slight cardiac enlargement, and those with marked, moderate, or slight hypertension in the right ventricle. These patients were then classified by grouping together those with grossly similar electrocardiographic patterns. A representative number of cases of the larger groups and all those with unusual patterns were selected for vectorcardiography. Thus, it was possible to gather a series of vectorcardiograms which represented almost all observable variations of the QRS sÊ loop that might be found in patients with known hypertrophy of the right ventricle. A study based on such selected material cannot contribute to the solution of the problem of what the earliest alteration in the cardiac electromotive field attributable to right ventricular hypertrophy might be because all patients displayed readily observable hypertrophy or enlargement. Nor is it possible, except by inference, to draw conclusions as to the changes which take place during increasing hypertrophy or dilatation. Precise anatomical correlations are not possible either because of the lack of post-mortem examinations.

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However, once the vectorcardiographic patterns had been gathered, it was possible to recognize with certainty the QRS sÊ loop associated with right ventricular hypertrophy, to delineate characteristic features, and to arrange all the vectorcardiograms in a continuous series ranging from the commonest and most characteristic to the most unusual and rare. It was also found that the system of lead placement used permitted a satisfactory correlation to be made between the vectorcardiogram of the frontal plane and the standard and unipolar extremity leads and between the horizontal plane projection of the QRS sÊ loop and circumferential chest leads. It was possible to distinguish the vectorcardiograms of patients with right ventricular hypertrophy from those seen in patients with right bundle branch block, unusual cardiac positions, or myocardial infarctions whose electrocardiograms revealed sufficient similarity to make a precise diagnosis impossible.

Vectorcardiography is a method of registration of the time course of the instantaneous electrical axes of the heart during depolarization and repolarization. A discussion of the details of lead placement, theoretical considerations, and technique of registration has been presented previously.[3] Briefly, a modification of the Duchosal-Sulzer system of lead placement has been used.[4] In the technique employed, bipolar leads were placed so as to form an X,Y,Z axis with the point of origin at the right posterior axillary line just below the diaphragm. Thus three orthogonal, independent leads were obtained, each approximately the same distance from the center of the heart. These were combined so as to form three planes, frontal, sagittal, and horizontal. The projection of the spatial vector loop in three planes was recorded from three oscilloscopes simultaneously. The technique is suited to wide routine use.

Regarding the correlation of the vectorcardiogram so obtained with standard and precordial electrocardiograms, it may be stated that the correlation is one of form and timing only, and not of amplitude. But this correlation is sufficiently useful to permit an accurate prediction of the chest lead pattern from the horizontal plane projection in all cases. In any case, it was felt that the unipolar precordial leads were graphic representations of the potential of points in the cardiac electrical field and as such were scalar projections of the cardiac vector upon a line running from the point of electrode placement through the electrical center of the heart. Since the chest lead pattern of the precordial area could be predicted from a vectorcardiogram whose component leads were at the patient's lumbar area, it was felt that they (the former) could not reflect potentials originating predominantly from parts of the heart directly beneath them. The precordial leads appeared to act as distant electrodes and, therefore, were subject to the same type of vector analysis as extremity leads.

MATERIAL AND METHODS

The patients were all obtained from the clinics and wards of The Mount Sinai Hospital. All patients were studied by the authors. Of the twenty-five patients selected for presentation, the diagnoses were tetralogy of Fallot in eight,

uncomplicated pulmonary stenosis in eight, interatrial septal defect in six, pulmonary hypertension with interatrial septal defect in two, and Eisenmenger's complex in one.

Cardiac catheterization and/or angiocardiography data were available in twenty-three patients. In the other two, the diagnosis and the presence of hypertrophy of the right ventricle were ascertained from fluoroscopy and clinical findings.

A Technicon three-channel electrocardiograph was used in conjunction with a triple Technicon vector oscilloscope. The horizontal, sagittal, and frontal plane projections of the spatial vector appear in all illustrations in that order, reading from left to right. The vector loop is interrupted 400 times per second by intensity modulation to permit time analysis. Electrocardiograms are taken at four times the conventional speed (10 cm. per second), unless otherwise indicated. The polarity and lead arrangement have been reported previously.[2] Positivity is directed anteriorly, downward, and to the left (observer's right) in the three planes.

The method of deriving standard and unipolar extremity leads from the central cardiac vector is too well known to require extensive description.[3] These leads are related most closely to the frontal plane projection of the spatial vector. If this frontal plane vector is placed at the center of an Einthoven triangle, the projections of the vectors at every instant upon the sides of the triangle determine the magnitude, form, and polarity of the electrocardiogram obtained in each lead. Lines drawn from the apices of the triangle to the center represent the axes of the unipolar extremity leads. Any projection of the vector upon these lines which lies between the triangle center and the apex will record a positive potential in the respective unipolar extremity lead. Any projection distal to the center will be recorded as a negative deflection.

The unipolar precordial leads may be derived from the horizontal plane vectorcardiogram in the same manner.[4] A line is drawn from the approximate position of the electrode on the chest through the approximate center of the heart; then another, perpendicular to it, is drawn also passing through the central point. The projection of the vector upon the axis of the electrode will determine the potential recorded at that point. A positive potential is recorded when the vector projects between the electrode and the central perpendicular line, and a negative potential when the projection is distal to it.

RESULTS

The vectorcardiograms are divided into three groups on the basis of similarity of vector patterns. Actually these groups represent only a segmentation of a continuous homogeneous series of patterns, which follows a rather simple, progressive change. The grouping in this fashion is one of convenience for descriptive purposes. A fourth group of miscellaneous patterns is included for completeness. The vectorcardiograms of this final group do not appear to be related to the others in any simple fashion. The electrocardiographic patterns to be found in each group will also be indicated.

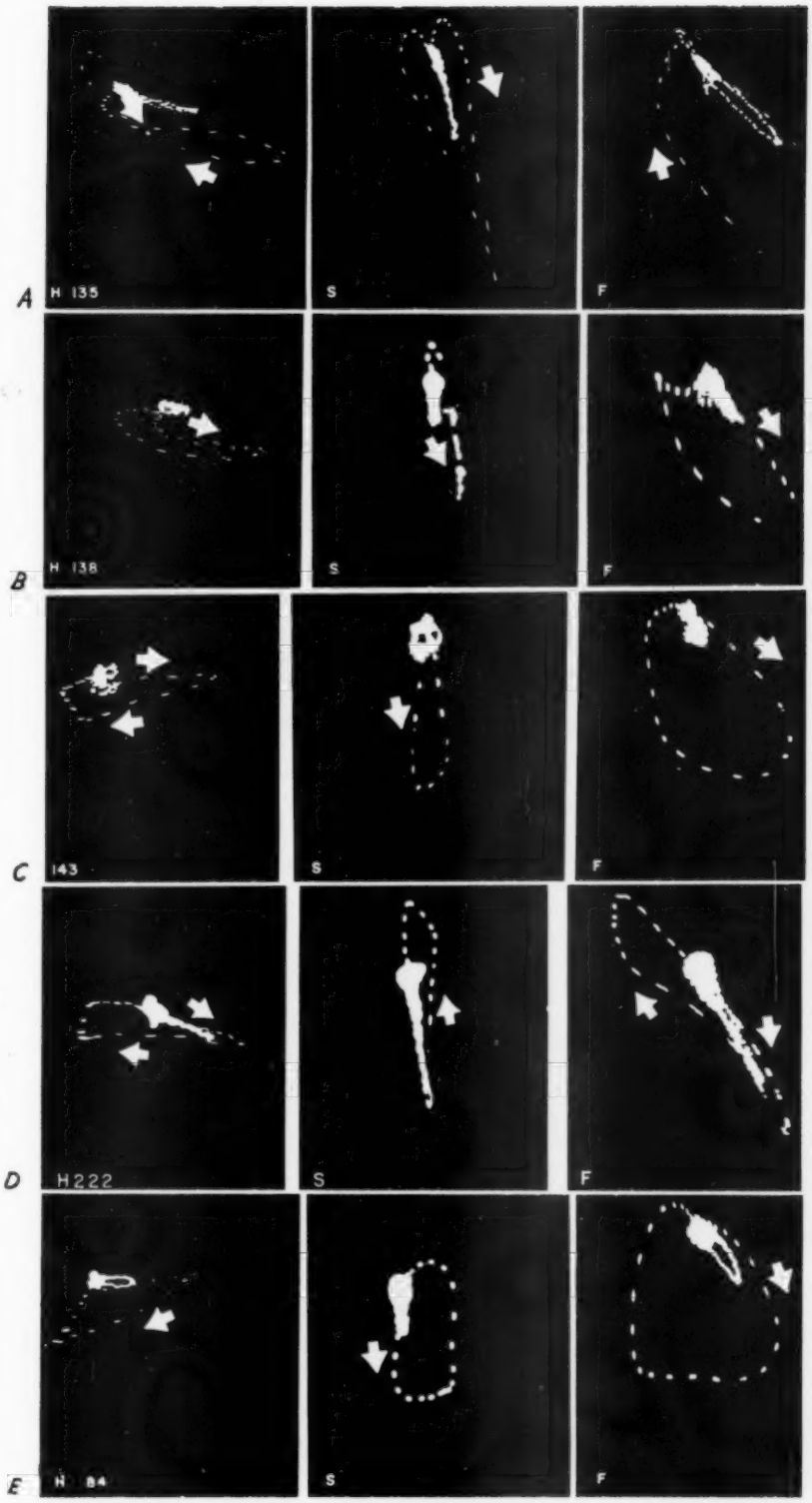

Fig. 1.—Spatial vectorcardiograms in right ventricular hypertrophy of mild degree. The highest right ventricular pressure found was 54 mm. Hg. The degree of right anterior orientation of the spatial vector loops is the least encountered in right ventricular hypertrophy.

Type I.—The vectorcardiograms of this group are shown in Figs. 1 and 2. These vector loops were obtained from three patients with uncomplicated pulmonary stenosis of a mild to moderate degree (Figs. 1,*A* and *E*, and 2) and three patients with interatrial septal defects (Fig. 1,*B*, *C*, and *D*). Right ventricular systolic pressure had been obtained in five of the six patients. The average of the five values was 45 mm. Hg, with a range of 39 mm. Hg to 54 mm. Hg.

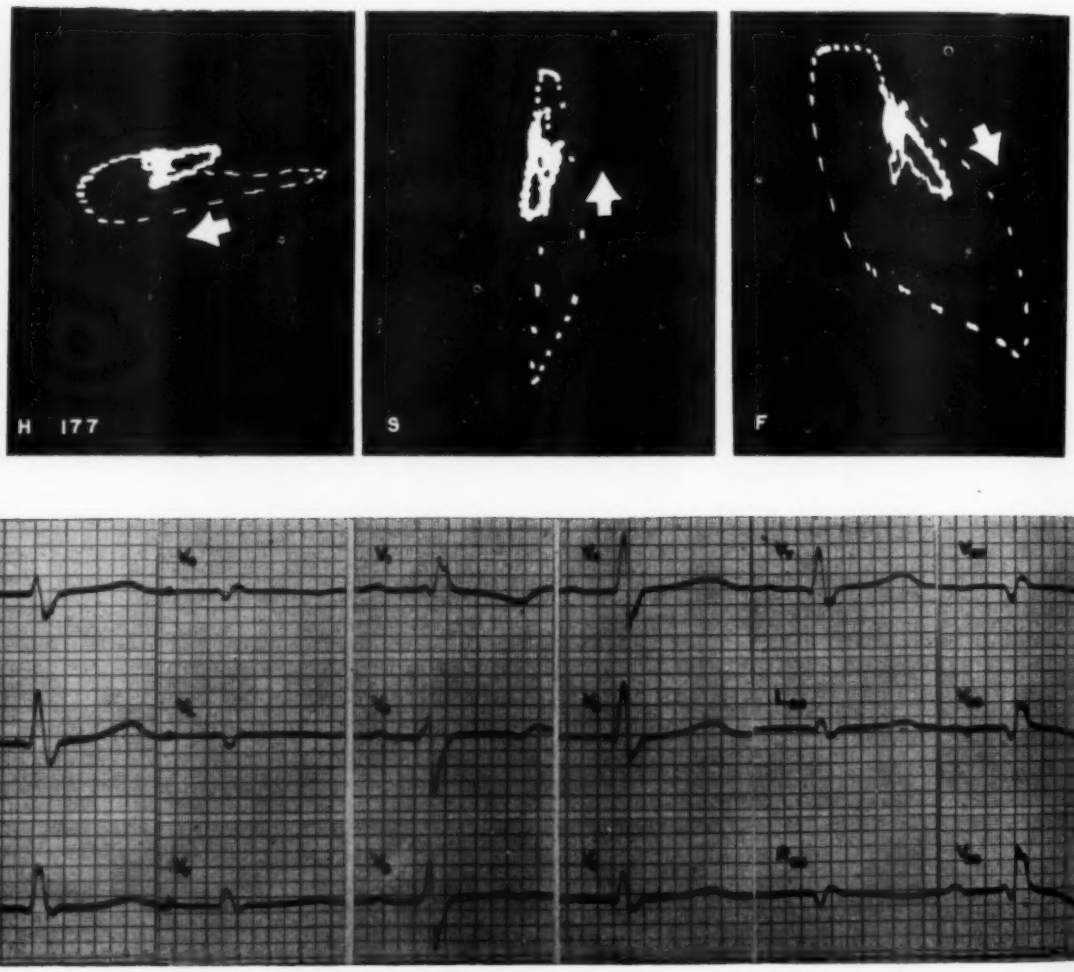

Fig. 2.—Right ventricular hypertrophy, type I. See text for detailed analysis and discussion.

The patients ranged in age from 3 years to 24 years. In two patients, no increase in the size of the transverse diameter of the heart was observable; there was moderate enlargement in three and marked enlargement in one. It was felt that this group contained those vectorcardiograms which displayed the least change which could be attributed to hypertrophy of the right ventricle due to congenital heart disease. They have been described in detail previously.[6]

The most characteristic pattern is shown in Fig. 2.

The vector loop pursues the following course. After leaving the isoelectric center spot, it travels to the right, upward, and anteriorly for a short time. A sharp turn is made, and the pathway proceeds to the left, downward, and slightly posteriorly. A 170 degree clockwise turn is then made, and the centripetal limb returns to isoelectricity by running to the right upward and anterior to the centrifugal limb. This same pathway is followed with but minor modifications in the other five vectorcardiograms shown in Fig. 1. The electrocardiogram shown in Fig. 2,*B* is the one obtained in the patient whose vectorcardiogram is presented as the prototype of this group. It shows a right axis deviation and a late R wave in Lead V_R. In precordial leads V_{R5} through V_1 an rSR′ complex is seen. The precordial leads V_5 through V_7 show a qRS pattern. An examination of the vectorcardiogram demonstrates that there is a close correspondence between the electrocardiogram and the projection of the horizontal plane vector loop on to a line connecting the approximate position of any chest electrode with the center of the heart. It may be readily seen that the initial portion of the vector loop which runs to the right, upward, and anteriorly will be reflected as a small positive deflection in Leads V_{R3} through V_3, as a negative deflection in Leads V_5 through V_8, and isoelectric in Leads V_4 and V_{R7}. The centrifugal limb which courses to the left, downward, and posteriorly produces negative deflections in leads from the right scapular area through V_1 and positive deflections in Leads V_2 through V_7. The final portion of the vector loop which returns to the right, upward, and anteriorly results in a return of positivity in Leads V_{R7} through V_1 and negativity in Leads V_2 through V_7. The correspondence between the complexes predicted from the vectorcardiogram and those actually observed is by no means absolute. Yet what is clearly demonstrated is that a definite relationship exists between the leads taken around the chest and the spatial loop.

There is a progressive alteration in the QRS sÊ loop from the first to the last case in Fig. 1, in that the centripetal limb assumes an increasingly anterior position. This is seen in the sagittal and horizontal plane projections. A further observation to be made is that the axis of the vector loop of the T wave lies close to the longest axis of the QRS loop. This relationship will be seen to alter with increasing right axis deviation of the QRS loop.

Type II.—The vectorcardiograms shown in Figs. 3, 4, 5, and 6 were obtained in six patients with tetralogy of Fallot (3,*B*, 4,*A*, 5,*A* and *B*, and 6), three patients with severe uncomplicated pulmonary stenosis (3,*D*, 4,*C*, and 5,*C*), two patients with marked pulmonary hypertension and interatrial septal defects (3,*C* and 4,*D*), and one patient with Eisenmenger's complex (3,*A*). Pressure readings were obtained in the right ventricle in five of the patients. The average right ventricular systolic pressure was 87 mm. Hg with a range of 70 to 115 mm. Hg. Only slight enlargement of the transverse diameter of the heart was noted in seven patients, and a moderate increase was present in the other five. The cardiac lesions of this group of patients were of the type which resulted in a rather marked degree of right ventricular hypertrophy.

As in the discussion of the type I QRS sÊ loops, one representative vectorcardiogram will be described, and the variations will be discussed (Fig. 6). It is inscribed in the right lower anterior octant. The direction of rotation is clock-

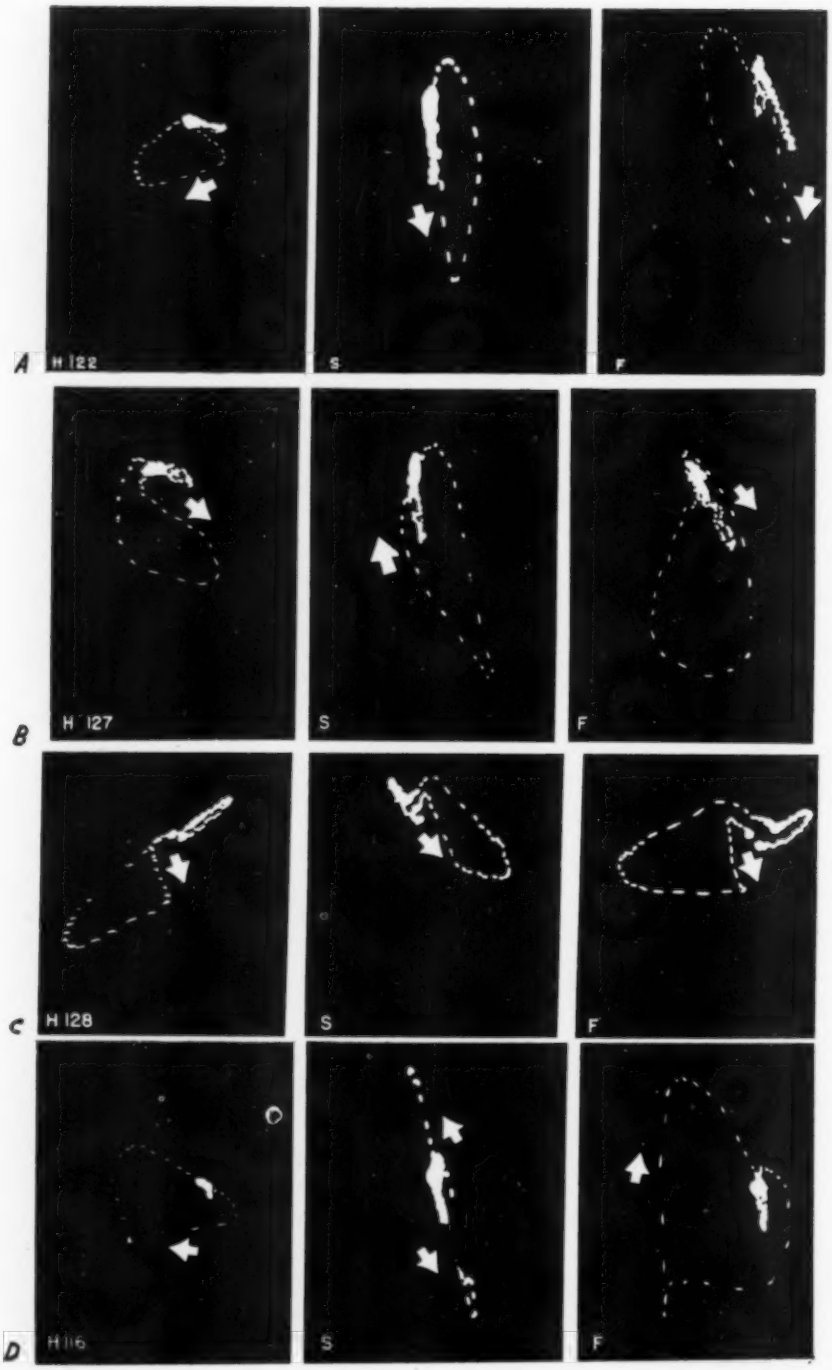

Fig. 3.—Spatial vectorcardiograms in right ventricular hypertrophy of advanced degree, type II. Note that the predominant orientation of the spatial vector loops A to D is in the right anterior lower octant.

wise in the horizontal and frontal planes and counterclockwise in the sagittal plane. An examination of the finer details shows that the QRS sÊ loop first proceeds to the right and anteriorly. This part of the vector pathway is much the same as that encountered in the type I vectorcardiograms. The pathway then proceeds to the left for approximately 0.01 second. Following this, a marked

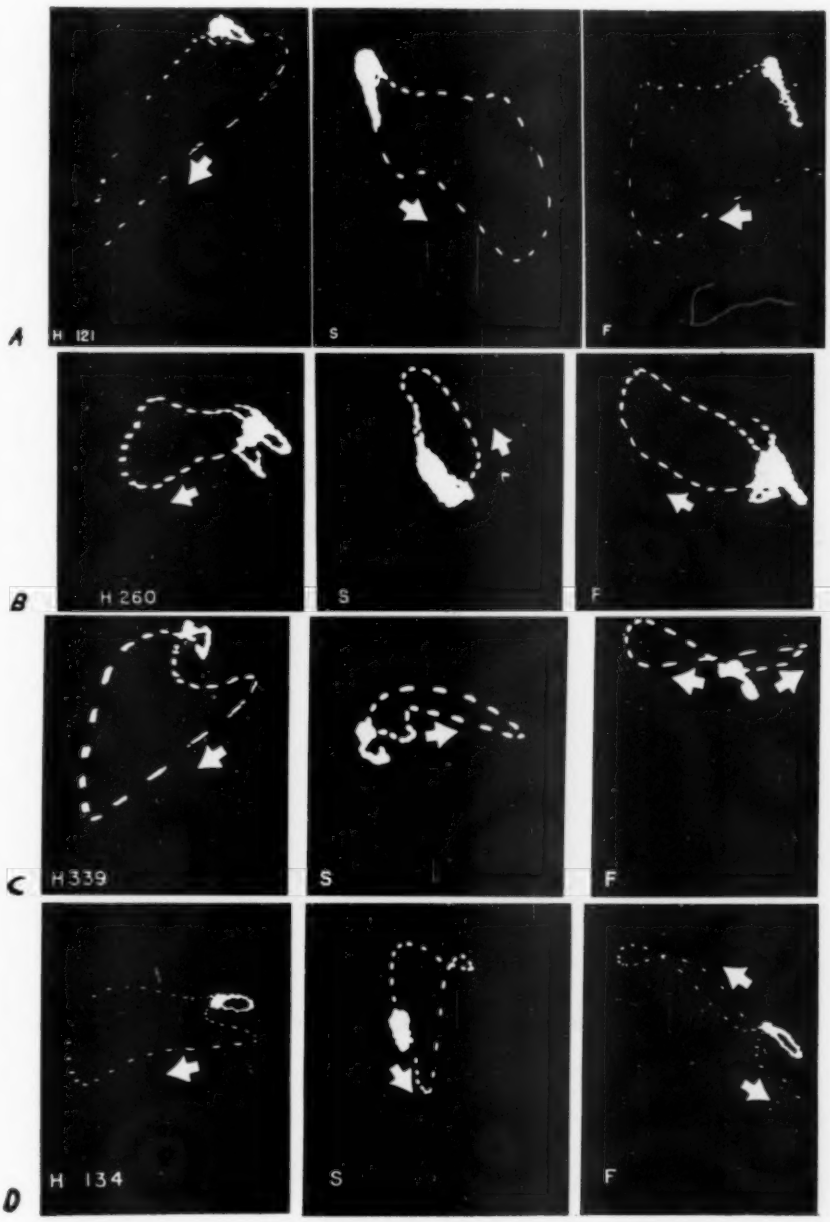

Fig. 4.—The predominant orientation of the spatial vector loops shows an increasing rotation toward the right anterior upper octant.

increase in the angular velocity of the vector is noticed as it bends to the right, downward, and anteriorly. The apex of the curve is reached and after a minute terminal crossed loop, the vector pathway proceeds upward and back to isoelectricity. The electrocardiogram shows a marked right axis deviation. Lead V_L is predominantly negative and V_F positive; Lead V_R shows a Q wave, followed

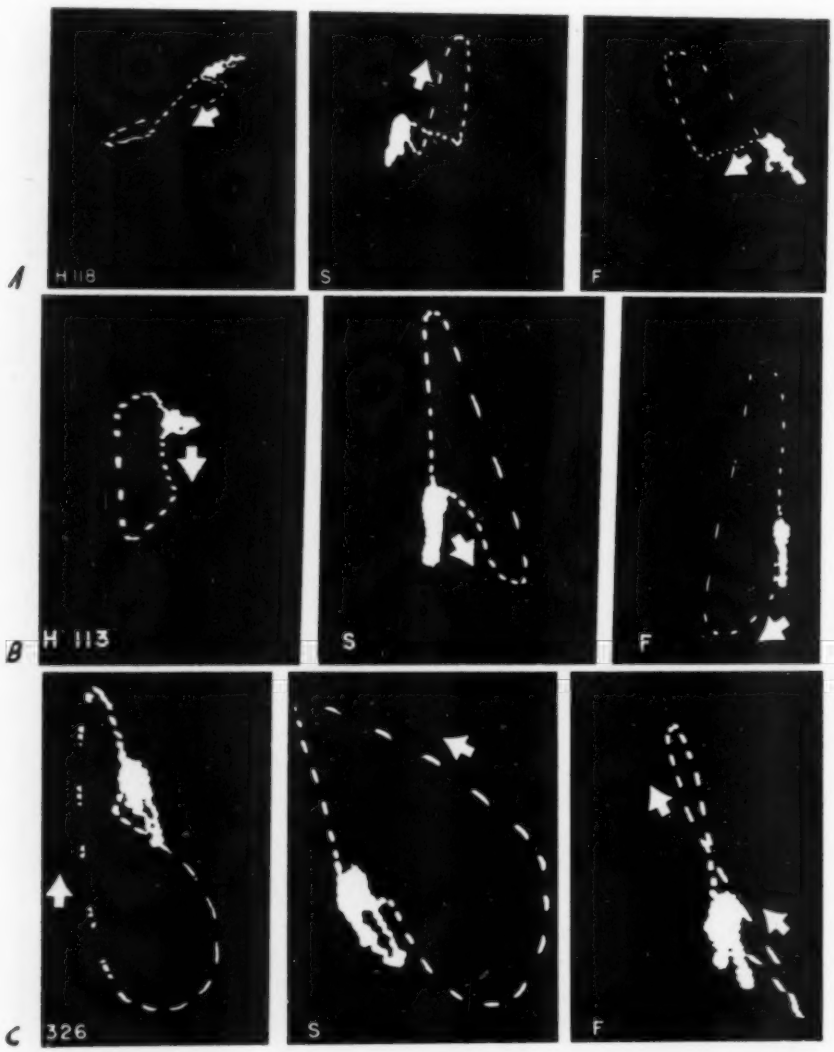

Fig. 5.—The predominant orientation of the spatial vector loops is in the right anterior upper octant. The vectorcardiograms in Figs. 3, 4, and 5 are arranged according to increasing degree of orientation from right anterior lower octant to the right anterior upper octant.

by a late, tall, and widened R wave. The form of these complexes corresponds closely to that predicted from the frontal plane vectorcardiogram. The precordial leads of the right side of the chest, V_{R8} through V_1, show tall R waves which are slurred on the upstroke with S waves of increasing depth. The precordial leads V_2 through V_8 are diphasic and the R waves decreased while S

waves increase in amplitude as the chest is circumscribed from right to left. The form of these complexes and their progressions are clearly indicated by the form of the horizontal plane vectorcardiogram.

The relationship between this QRS sÊ loop and those of type I is evident. The same features are present, a small right anterior arc followed by a segment extending to the left and downward followed by a return of the centripetal limb

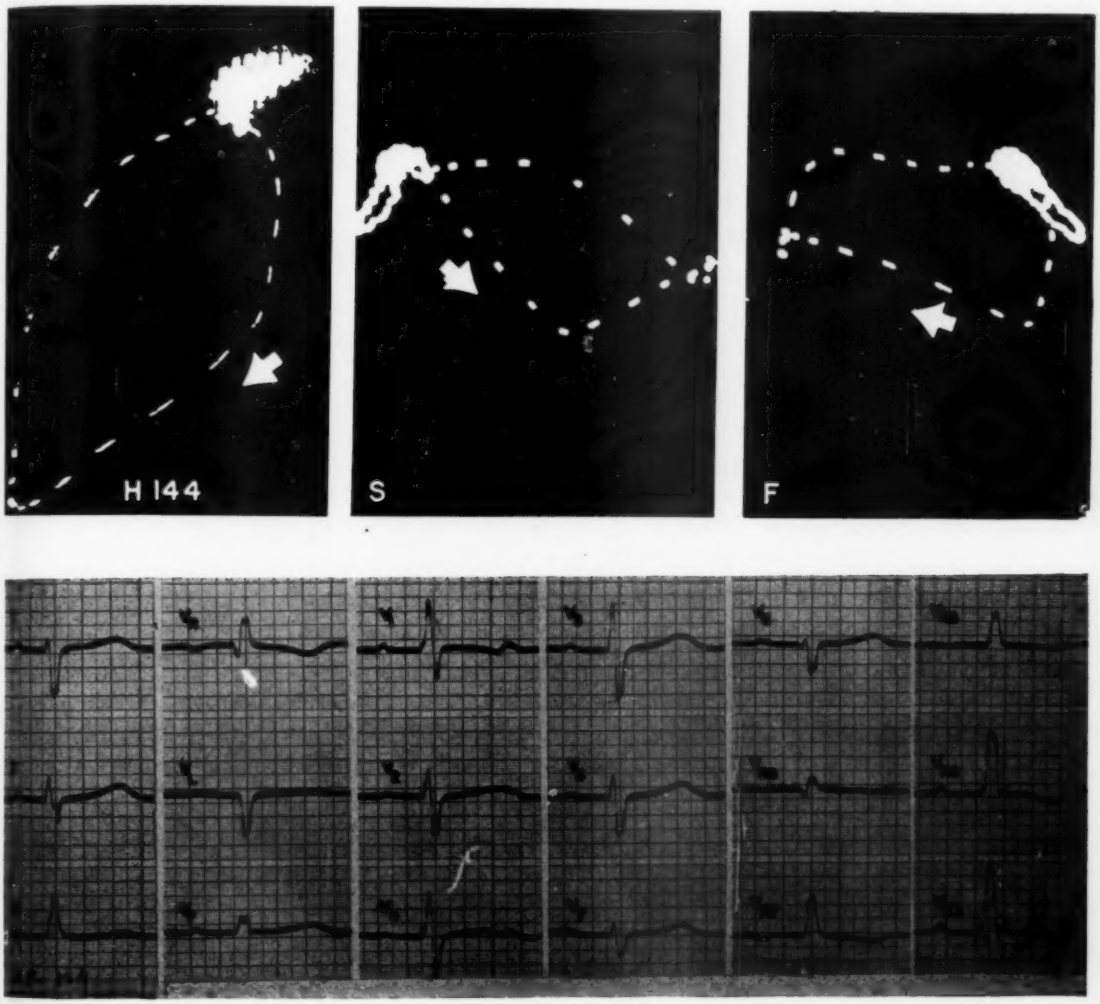

Fig. 6.—Right ventricular hypertrophy, type II. See text for detailed analysis and discussion.

to the right and anteriorly. This is apparently the basic pathway of the QRS sÊ loop associated with right ventricular hypertrophy. The changes from the type I vectorcardiogram to this present type are: (1) the orientation of the loop is deviated to a further right anterior position; (2) the segment of vector pathway which extends to the left and downward becomes much shorter; and (3) the returning or centripetal limb assumes a more and more anterior position.

The vectorcardiograms of this present series show an alteration in form and orientation which appears to be an extension of that described occurring between type I and type II. A glance at the frontal plane vectorcardiograms in order will show a gradual deviation of the main axis of the loop to the right. This deviation proceeds in a clockwise fashion (as seen by the observer) about the anteroposterior axis. The clockwise swing finally brings part of the vector loop into the right, upper quadrant. This results in the recording of increasingly deep S waves in all three standard leads. The last two vectorcardiograms were obtained in patients whose electrocardiograms showed predominantly negative deflections in the three standard leads. It may also be seen that the vector loop comes to lie increasingly in the horizontal plane and assumes a position with the greatest surface circumscribed perpendicular to the frontal plane. It is as though the apex of the vector loop were lifted up.

Electrocardiograms of right ventricular hypertrophy which contain a qR type of complex in Leads V_{R3} or V_1 are explained by the fact that the initial (septal) vector is perpendicular to the plane of the electrode. If carefully timed, it will be found that a short isoelectric period precedes the onset of the q. A vectorcardiogram obtained in such a case is shown in Fig. 3,*D*. A further significant feature to be noticed is that the axes of the T loops and QRS loops become increasingly divergent. There is some significance to this observation since it would be difficult to reconcile it with any theory which proposes that the alteration in electrical fields observed in patients with hypertrophy of the right ventricle is predominantly or solely due to anatomical rotation.[7]

The electrocardiograms and vectorcardiograms of this second group of patients are the ones most characteristically associated with hypertrophy of the right ventricle. However, since the fundamental vector pathway is the same as that seen in the first type described, it is believed that the differences observed are merely of a quantitative nature and that each vector is equally representative of hypertrophy of the right ventricle.

Type III.—The vectorcardiograms shown in Figs. 7 and 8 were obtained from two patients with severe pulmonary stenosis (7,*A* and 8) and two patients with large interatrial septal defects and marked cardiac enlargement (7,*B* and *C*).

In the cases with marked pulmonary stenosis, the right ventricular systolic pressure in the first was 70 mm. Hg and 136 mm. Hg in the second. Both hearts were only slightly enlarged in their transverse diameter. Angiocardiograms were obtained in both patients, and no unusual cardiac position or rotation whatever was discerned.

The relationship between these two vector loops and the final ones of the previously described group is apparent.

The initial part of the vector pathway is obscured by the T loop and the fine details are difficult to see. However, the loop appears to run slightly to the right and anteriorly in both, then vertically downward and slightly to the left. The major portion of the loop is formed by a centrifugal ascending limb which lies slightly to the right of the midline in 7,*A* and slightly to the left in 8. Thus, the electrocardiogram shows an rS in the three standard leads in 7,*A* and an

Rs_1, rS_2, rS_3 in 8. This latter patient therefore shows left axis deviation in the presence of marked right ventricular hypertrophy.

The horizontal plane vectorcardiogram is predominantly posterior in 7,*A*. The precordial electrocardiogram therefore displays a small r deep S wave in Leads V_1 through V_7. The vector loop is anterior in 8, and the precordial

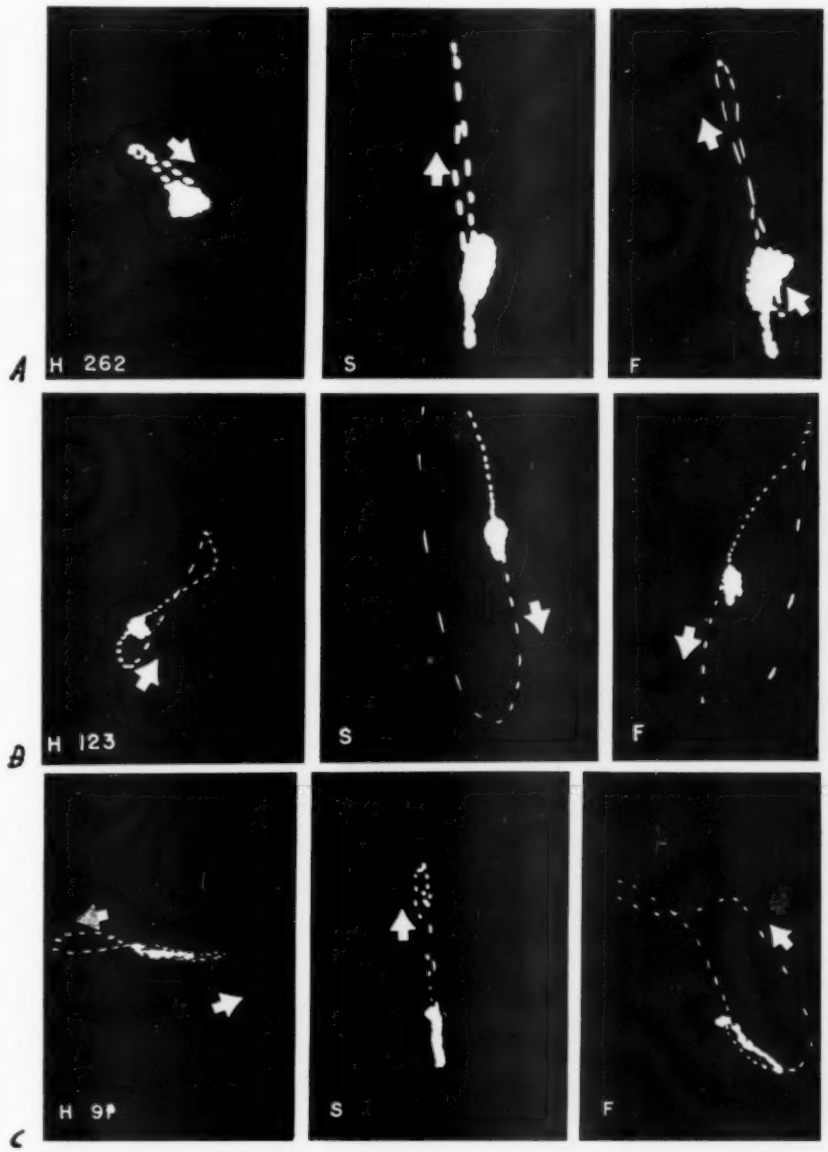

Fig. 7.—Spatial vectorcardiograms in right ventricular hypertrophy of severe degree. *A*, Predominant orientation of the vector loop is in the right upper posterior octant. *B*, Predominant orientation of the vector loop is in the left upper and lower posterior octant. *C*, Main orientation is along the central frontal plane to the left and up.

electrocardiogram consists of an rSR′ complex in Leads V_{R5} through V_1. The correspondence between the standard and unipolar extremity lead electrocardiogram and the frontal plane vectorcardiogram is close. In the horizontal plane the projection of the vector loops onto the axes of the precordial leads does correspond with the form of the QRS complex in respect to timing and polarity.

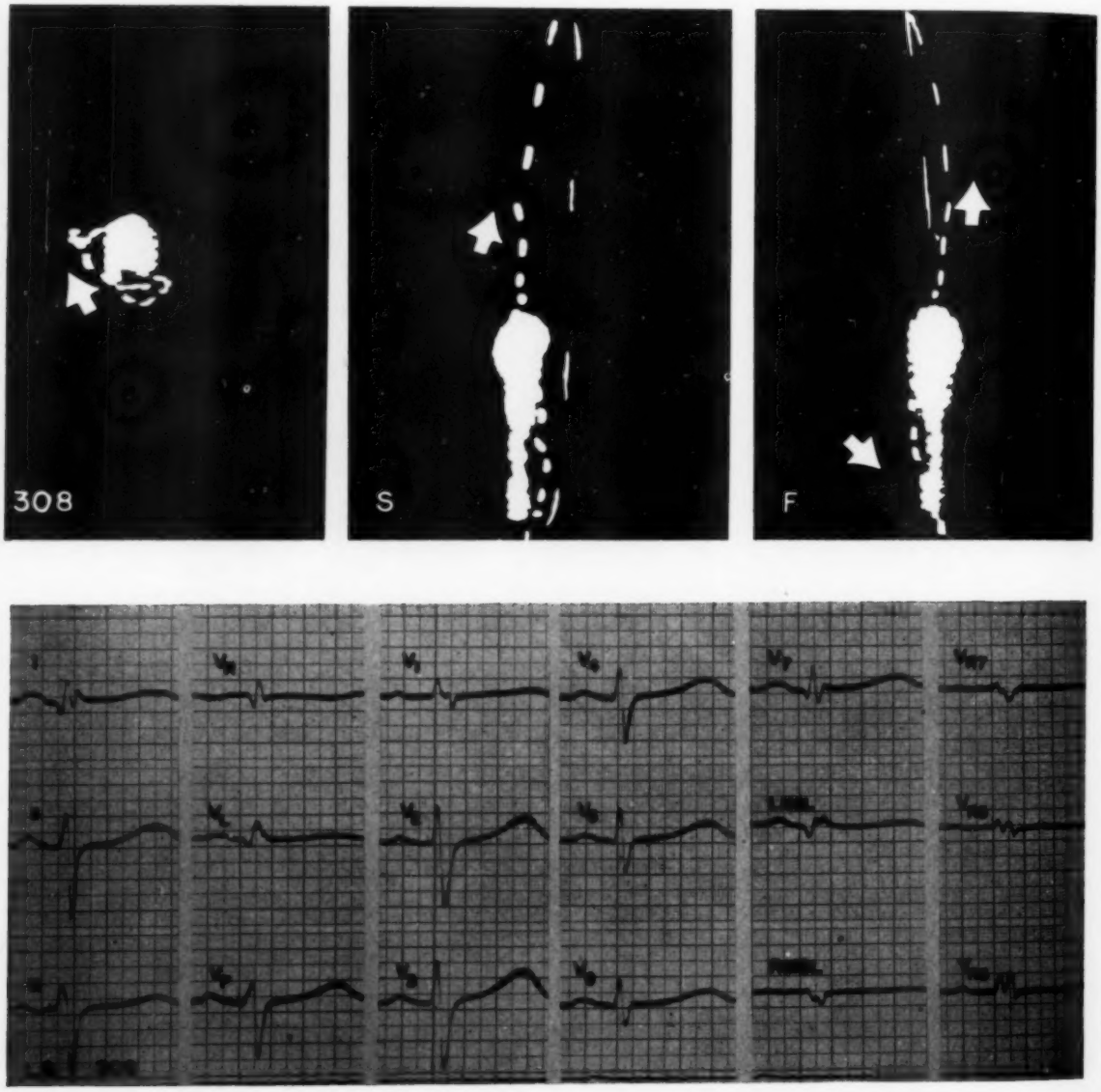

Fig. 8.—Right ventricular hypertrophy, type III. See text for detailed analysis and discussion.

Vectorcardiograms 7,*B* and 7,C were obtained in two patients with interatrial septal defects and large hearts. The direction of rotation in the frontal plane is counterclockwise. Both vector loops lie predominantly in the left,

upper quadrant, and therefore the standard leads show left axis deviation. The horizontal plane vectorcardiogram of 7,*C* is distributed both to the left and right of the midline, and the unipolar precordial leads are therefore biphasic all around the chest. The vector loop 7,*B* lies in the left, posterior quadrant, and predominantly positive complexes are found only in leads from the left, lateral side of the chest. These vectorcardiograms are the result of a marked clockwise rotation of the electrical position of the heart, though the anatomical position is unchanged. The axis of the T-wave vector loop is almost 180 degrees divergent from the longest axis of the QRS sÊ loop in all four cases. It is felt

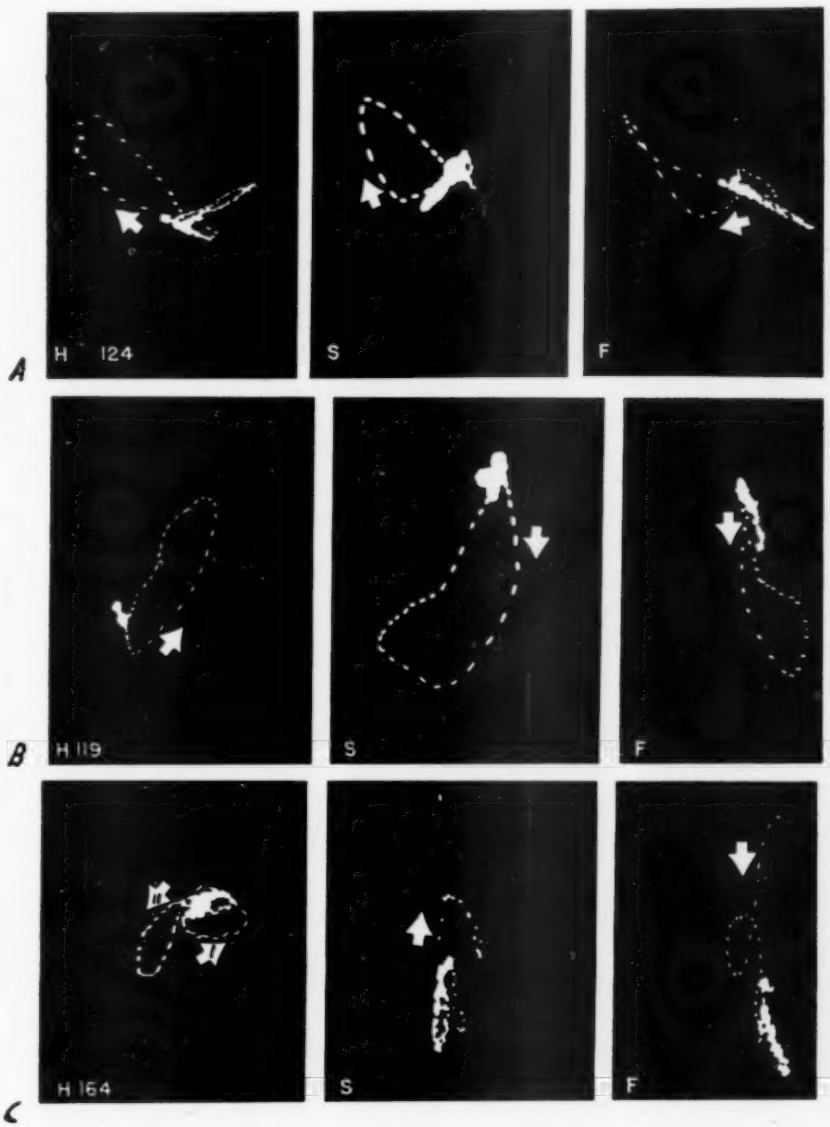

Fig. 9.—Spatial vectorcardiograms in right ventricular hypertrophy. There are unusual orientation and configuration of loops. None are closely related to types I to III.

that these vectorcardiograms are the result of an unusual pattern of hypertrophy resulting in a vertically upward orientation of the vector loop and that this orientation is the final result of an increasing clockwise swing of the spatial vector which produces all intermediate positions between type I and those described as type III.

Type IV.—In this group are three vectorcardiograms (Fig. 9) which were all obtained in patients with well-authenticated right ventricular hypertrophy. The vector loops do not appear to be related, in any simple fashion, to those previously described. In Fig. 9,*A*, a vectorcardiogram is shown which is inscribed in the right, upper posterior quadrant. Though right axis deviation is present, the precordial leads V_1 to V_6 all show small r deep S waves.

Fig. 9,*B* is the vectorcardiogram of a patient with a tetralogy of Fallot. As far as can be seen, this is a normal vectorcardiogram except for the fact that the loop in the horizontal plane projection extends much farther posteriorly than do projections of normals of this age. The electrocardiogram likewise shows no evidence of right ventricular hypertrophy. The vectorcardiogram shown in Fig. 9,*C* was obtained in a patient with an interatrial septal defect. It is unusual for several reasons. The major portion of the projection of the spatial loop to the frontal plane is in the left upper quadrant. There is then left axis deviation. This is not dissimilar to the last two vectorcardiograms of the previous group. However, the descending centripetal limb describes a wide secondary circle before returning to isoelectricity. This secondary circle lengthens the QRS interval to 0.10 second which is long for a child 9 years old. The increased deviation of the QRS interval is due to a wide, shallow S wave in Lead I which is, in turn, a reflection of this secondary looping of the descending limb. It is seen in the sagittal plane as an anterior extension and in the horizontal plane as a secondary loop extending to the right and anteriorly. It is reflected in the electrocardiogram as a notching of the R wave in V_R and of the S wave in V_F, as an RSR′ complex in V_{R3} and V_1, and as a notching of the R wave in V_2 and V_3. It is felt that this vectorcardiogram represents a minor conduction abnormality in addition to right ventricular hypertrophy.

DISCUSSION

The vectorcardiographic analysis has served three purposes in this study. The fundamental vector pathway associated with hypertrophy of the right ventricle and the relationship between the various vector pathways observed have been described and discussed. The close correlation between electrocardiogram and vectorcardiogram has been indicated. It remains only to discuss the vectorcardiographic distinction between right ventricular hypertrophy and positional changes, right bundle branch block or myocardial infarction.

The vectorcardiogram may be shifted in a clockwise direction about the anteroposterior axis in a person with a markedly vertical heart, thereby producing a right axis deviation in standard leads. The distinction between positional axis deviation and ventricular hypertrophy is easily made by examination of the horizontal projection. The vector loop in this projection is normal in rotation

(counterclockwise), form, and orientation in normal individuals with vertical hearts, but is characteristically altered in patients with hypertrophy of the right ventricle. We have never observed the centripetal limb to return anterior to the centrifugal limb in any patient with a normal, vertically rotated heart.

Occasionally, precordial electrocardiograms in normal individuals display a tall R small s or equiphasic RS complex in V_1. This is seen commonly in children below the age of 10 years, and it has been found that these, too, offer no problem of differentiation by vectorcardiograms. The horizontal plane projection of the vectorcardiogram is again normal in rotation (counterclockwise) and orientation in these normal children. However, the distinctive feature of these vectorcardiograms is that the initial portion of the vector loop, which proceeds anteriorly and to the right, is elongated and forms a wide loop extending to the right and anteriorly. This accounts for the tall R in Lead V_1. However, the remainder of the loop is normal, and the centripetal limb is posterior to the centrifugal one. This will be discussed in greater detail in a future communication. The relationship of pulmonary heart disease and mitral stenosis to the vectorcardiogram will also be reported on in the future.

The QRS sÊ loops obtained in atypical right bundle branch block (Wilson block) and the distinction between them and those of right ventricular hypertrophy have been discussed in a previous report by us.[6] Briefly, the spatial vectorcardiogram of bundle branch block is characterized by an irregular, terminal portion of the loop wherein the angular velocity is very markedly reduced and the time markers very closely spaced. This irregular terminal segment assumes a right anterior orientation regardless of the orientation of the remainder of the spatial loop. As such, it represents a departure from the "plane of predilection" of the major portion of the loop.[9] This terminal segment accounts for the wide, shallow S in Lead I, the tall R in V_R, and the R′ wave of the rSR′ complex seen in Leads V_{R3} or V_1. Distinction between patients with atypical right bundle branch block and those with moderate degrees of right ventricular hypertrophy can be made only by vectorcardiography.

Patients with myocardial infarctions occasionally have electrocardiograms which show right axis deviation or a tall R wave in Lead V_1.[10] Detailed analysis of this is given in another publication.[11] However, the spatial vectorcardiogram in these patients is generally bizarre and irregular. Though the vector loop is inscribed in the right, anterior, lower octant, the form and direction of rotation are entirely different from those of right ventricular hypertrophy. The distinction offers no difficulties.

The vectorcardiograms reported here were obtained by one particular system of lead placement. This system was selected because of theoretical considerations, the convenience of application, and the correlation obtainable with the standard and precordial electrocardiogram. There is no claim made that these represent the only true visualization of the cardiac electromotive field. It is realized that the body is not a precise geometrical figure, that the heart is not at the exact center of the leads, that tissue conductivity varies, and that electrodes vary in the plane of their location and in their distance from the heart.

In spite of these variables, the correlation between electrocardiogram and vectorcardiogram is close. Moreover, gross as it may be, analysis of vector pathways offers information about the electrical field of the heart that can be obtained from electrocardiography only with great difficulty or not at all. Spatial vectorcardiography allows simple presentation of the electrical forces generated by the heart in space.

CONCLUSION

1. A study was made of the vectorcardiograms obtained in patients with varying degrees of well-authenticated hypertrophy of the right ventricle associated with congenital cardiac disease.

2. It was possible to recognize with some certainty the QRS sÊ loops associated with right ventricular hypertrophy and to describe certain characteristic features.

3. The characteristic features of the QRS sÊ loops found in patients with hypertrophy of the right ventricle made it possible to distinguish these from the vectorcardiograms obtained in patients with a markedly vertical electrical position or atypical right bundle branch block. The vectorcardiograms of children whose precordial electrocardiograms displayed tall R waves in V_1 and of patients with myocardial infarction showing the same feature were likewise found to be easily distinguishable from those of true hypertrophy of the right ventricle.

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DIFFERENTIATION BETWEEN PAROXYSMAL AURICULAR TACHYCARDIA WITH PARTIAL A-V BLOCK AND AURICULAR FLUTTER

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MANY authors[1-7] have described the difficulty of differentiation between auricular flutter and auricular tachycardia. The separation is even more troublesome when the latter condition is associated with partial A-V block. In fact, auricular heart rates between 180 and 270 beats per minute with varying degrees of partial heart block have been interpreted by some authors as auricular flutter[7] and by other authors[8-11] as paroxysmal auricular tachycardia. Prinzmetal and associates[12] have suggested that the basic mechanism of flutter and auricular tachycardia is a single ectopic focus and is the same for both conditions. They found, by means of high-speed cinematography, that the rate of auricular contractions was slower in paroxysmal tachycardia than in flutter, and this was the chief difference between the two.

Decherd and co-workers[10] reported forty case studies of auricular tachycardia with partial A-V block. Of these patients, twenty-two died during the period of hospitalization. This relatively high mortality was confirmed by Benchimol and Laransa[11] in a smaller series of six cases. This alarmingly high mortality rate would indicate that paroxysmal tachycardia with A-V block is frequently associated with advanced heart disease. Barker and associates[9] noted that the degree of disability in paroxysmal tachycardia with partial A-V block is often greater than in paroxysmal tachycardia without block.

CRITERIA FOR DIFFERENTIATION BETWEEN PAROXYSMAL AURICULAR TACHYCARDIA AND FLUTTER

The criteria advanced by Lewis[1] for differentiation between common paroxysmal auricular tachycardia and auricular flutter are not adequate when the tachycardia occurs with A-V block.[10] Most of the criteria suggested are relative rather than absolute. Scherf and co-workers[7] interpret the auricular tachycardia produced by local application of aconitine to the auricle in dogs as auricular flutter because of the frequent change of the auricular tachycardia into auricular

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fibrillation, the increase of the auricular rate by vagal stimulation, and the similarity in the polarity and contour of auricular deflections. Spontaneous transitions of paroxysmal tachycardia to auricular flutter and vice versa, although comparatively rare, have been observed repeatedly, in fact as far back as 1915 by Parkinson and Mathias.[14] Decherd and associates[10] found in a few of their patients, on different occasions, all three types of auricular arrhythmias: flutter, fibrillation, and paroxysmal tachycardia. They concluded that the presence of flutter at one time does not rule out the possibility of tachycardia at another time. A summary of the criteria which might be helpful for differentiation has been given by Barker and associates[9] and by Decherd and associates.[10]

The most important criterion in differentiating auricular tachycardia from flutter is the contour of the P-P or T-P intervals. In the tachycardia these intervals are briefly isoelectric, while in flutter most leads show continuous motion of the galvanometer (Lewis[13]). However Lewis, Drury, and Iliescu,[15] in 1921, published as auricular flutter a case with an auricular rate of 245 per minute, 2:1 A-V block, and clearly isoelectric P-P intervals. Scherf[16] minimizes the importance of isoelectric P-P or P-T intervals. He noticed that the form of the P wave did not change when, in the tachycardia produced by aconitine, the rate was slowed down by local application of a cold stimulus and rapidly increased after its removal. This appears to be dissimilar to the pattern of auricular flutter in the human being.

The auricular rate is of importance for the interpretation, since, as a rule, it is higher in flutter than in paroxysmal tachycardia. Lewis[11] gave as normal limits for auricular flutter in man from 200 to 350 oscillations per minute. An auricular rate, rapid but below 200, is usually auricular tachycardia and above 300 is usually auricular flutter. Unfortunately, the range limits for flutter and paroxysmal tachycardia overlap widely. Lewis published a case of auricular paroxysmal tachycardia with a rate of 290 per minute. In Decherd's[10] material the fastest auricular rate in paroxysmal tachycardia was 260, and in Barker's[9] series it was 275.

RESULTS

This study consists of ten patients with auricular tachycardia with A-V heart block of second or third degree all showing flat or nearly isoelectric P-P intervals. Due to the presence of partial A-V block, the auricular activity is apparent and mensurable, whereas with 1:1 conduction the P waves often are buried in the excursions of the ventricular complexes. The case histories are given in the appendix. The terms "auricular flutter" and "paroxysmal auricular tachycardia with A-V block" are used for descriptive purposes. The question of their identity will be discussed in a later part of this paper.

In spite of the criteria suggested for differentiation between auricular flutter and paroxysmal tachycardia, a definite interpretation often is impossible within the overlapping rates. Fig. 1 may serve as an illustration. The auricular rate of patient Hlu was about 190 per minute with a 4:1 A-V block. The P-P intervals

in Lead III were not truly isoelectric, although the slope was very slight. The interpretation is open to arbitrary judgment since the P-P intervals in V_1 were isoelectric.

In patient Dov, the auricular rate was 222 per minute with a 4:1 partial A-V block (Fig. 2). In Leads III, aV_L and aV_F, the P-P intervals were isoelectric.

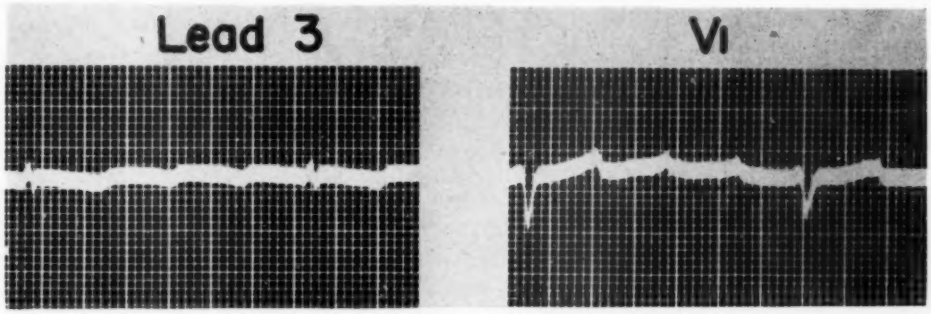

Fig. 1.—Patient Hlu. The auricular rate is 190 per minute, with a 4:1 A-V block. The P-P intervals show a very slight slope.

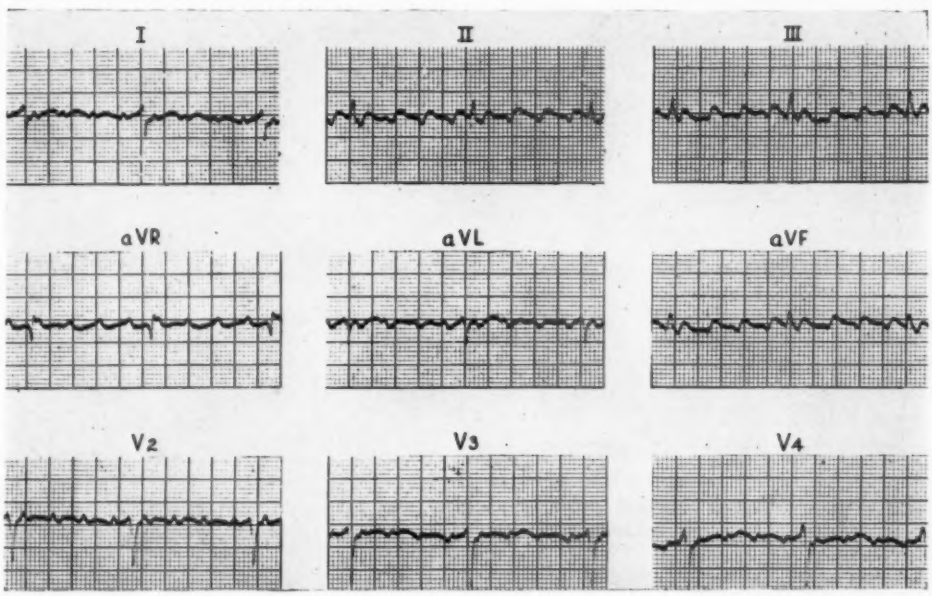

Fig. 2.—Patient Dov. The auricular rate is 222 per minute with a 4:1 A-V block. The P-P intervals are isoelectric in Leads III, aV_L, and aV_F; a slight slope appears in Leads II and aV_R and a low convex deflection in Leads I, V_2, V_3, and V_4.

In Leads II and aV_R the P-P intervals were not truly isoelectric, although the slope was slight. The P waves were distinctly superimposed on this trend and abnormal in direction. In Leads I, V_2, V_3, and V_4 the distinct P waves of 0.06 second duration were separated by slightly convex P-P intervals. Although the P-P intervals were not isoelectric in some leads, they did not show the typical

pattern of flutter waves. One might wonder whether they represented auricular T waves. This tracing is not typical for classical flutter nor for paroxysmal auricular tachycardia with A-V block.

The auricular rate in both Mac and Ste (Fig. 3) was 316 per minute. The contour of the P waves was normal except the reversal in direction in Lead II of Mac. The P-P intervals were isoelectric. Both patients were considered as having paroxysmal auricular tachycardia with a partial A-V block of 2:1. The interesting feature of the tracings in Fig. 3 is the high auricular rate at which this phenomenon can be observed.

Coarse auricular fibrillation and paroxysmal tachycardia occurred in patient Dou on different occasions (Fig. 4, first row). In this patient paroxysmal auricular tachycardia was associated with complete A-V block which is unusual.

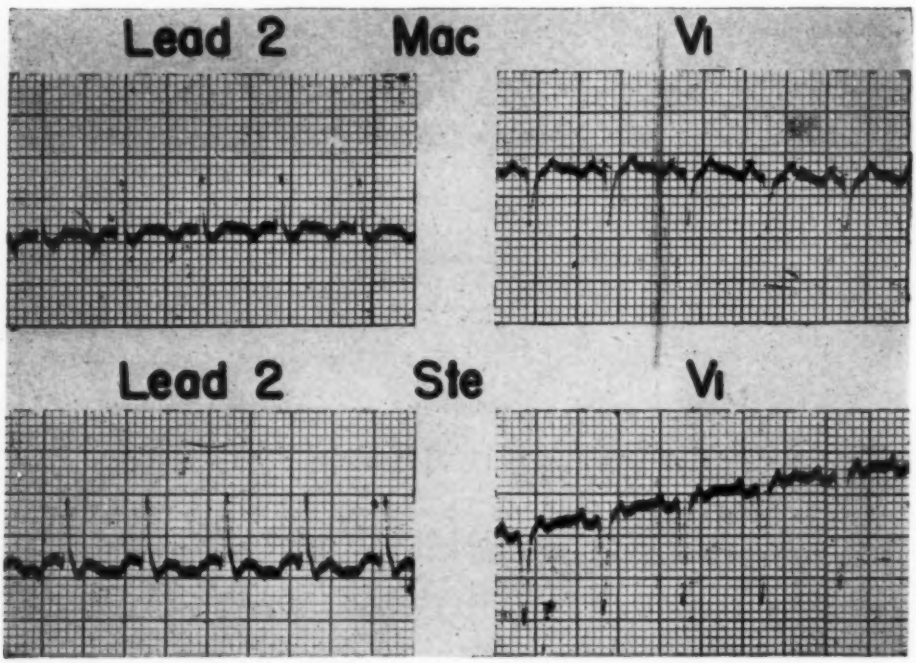

Fig. 3.—The auricular rate is 316 per minute with a 2:1 A-V block and isoelectric P-P intervals in two patients.

Patient Der (Fig. 4) ran the gamut of supraventricular rhythms. Sinus rhythm is shown on April 24, 1950, coarse auricular fibrillation on April 5, 1950, rather regular auricular flutter on March 27, 1950, and paroxysmal auricular tachycardia with 2:1 A-V block on Feb. 22, 1950, increasing occasionally to 3:1 block on April 24, 1950. The auricular rate with the tachycardias of February 22 and April 24 was 240, the P waves were of normal contour, and the P-P intervals, especially on April 24, were isoelectric.

Fig. 5 shows a spontaneous change of the direction of the P waves in Leads I, II, and III in patient Der without change of the auricular rate. The P-P intervals in Leads I to III were isoelectric with normal monophasic P waves. The

rate was extremely high (400 per minute). To our knowledge, it is the highest rate of paroxysmal auricular tachycardia with partial A-V block yet observed. In V_1, typical diphasic flutter waves appeared at the same auricular rate. This might suggest that flutter was present throughout the whole tracing, with a vector unfavorable for projection on the frontal plane. However, the isoelectric P-P intervals are usually very well recorded in V_1 (see Fig. 3), and it would be surprising if such large flutter waves as those in V_1, were not recorded in at least one of the standard leads. It is possible that in V_1 auricular flutter had replaced the paroxysmal auricular tachycardia with partial A-V block (mostly 2:1) shown in Leads I to III.

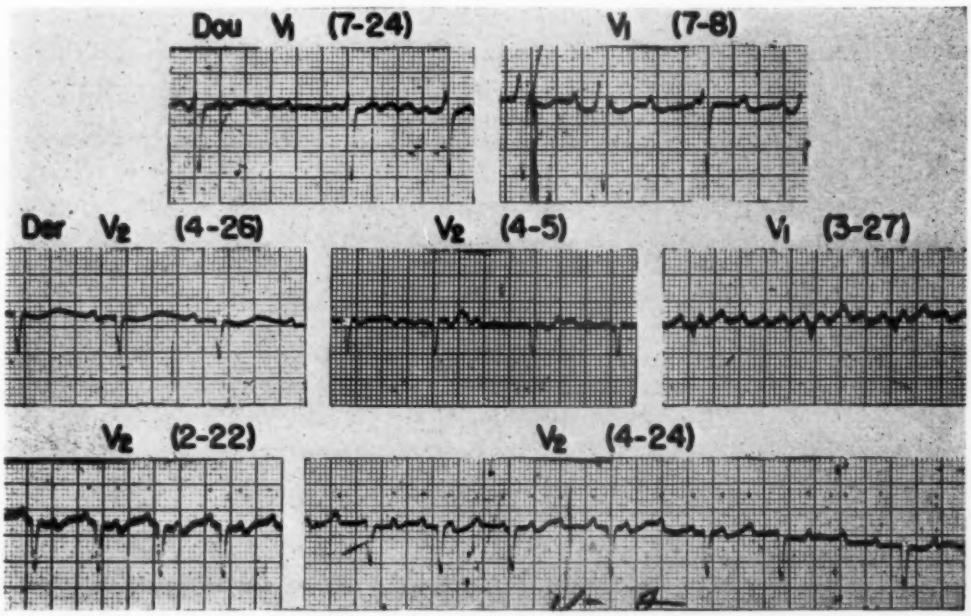

Fig. 4.—There are auricular fibrillation and paroxysmal auricular tachycardia with complete A-V block in patient Dou (first row). There are sinus rhythm, auricular fibrillation, impure auricular flutter, and paroxysmal auricular tachycardia with 2:1 block and with varying A-V block in patient Der (second and third rows).

In one patient (Bea, Fig. 6) with a supraventricular paroxysmal tachycardia at a rate of 158 per minute, vagal stimulation by means of carotid sinus pressure produced 2:1 block without change of the auricular rate. No distinct P waves could be seen before application of pressure, but regular P waves appeared immediately after, with a gradual shortening of the P-R intervals from 0.23 to 0.19 second in the following four beats. In this case carotid sinus pressure converted a common type of paroxysmal tachycardia into paroxysmal auricular tachycardia with A-V block.

In patient Hol (Fig. 6), carotid sinus pressure increased for a brief period the degree of A-V block from an initial 2:1 block to 3:1. The auricular rate increased from 286 to 316 per minute. Brief isoelectric intervals could be seen preceding the P waves before application of pressure. The P-P intervals after

carotid sinus pressure were so short that they were not clearly isoelectric. However, the P waves had normal contour. We assume that, similar to Bea, carotid pressure affected only the A-V conduction, not the basic type of tachycardia.

Typical auricular flutter was observed in patient Kal on various occasions, as shown in Lead II (Fig. 7*A*), at an auricular rate of 300 per minute and a 2:1 A-V block (May 21, 1950). Six months later, auricular rhythm was observed at a rate of 268 per minute with 2:1 A-V block (Nov. 24, 1950, Fig. 7*B*). The P-P intervals in Leads II and III approached but did not attain isoelectric levels. True isoelectric P-P intervals appeared in the chest leads. Three days later, Leads II and III showed impure flutter at about the same auricular rate with isoelectric P-P intervals in most chest leads.

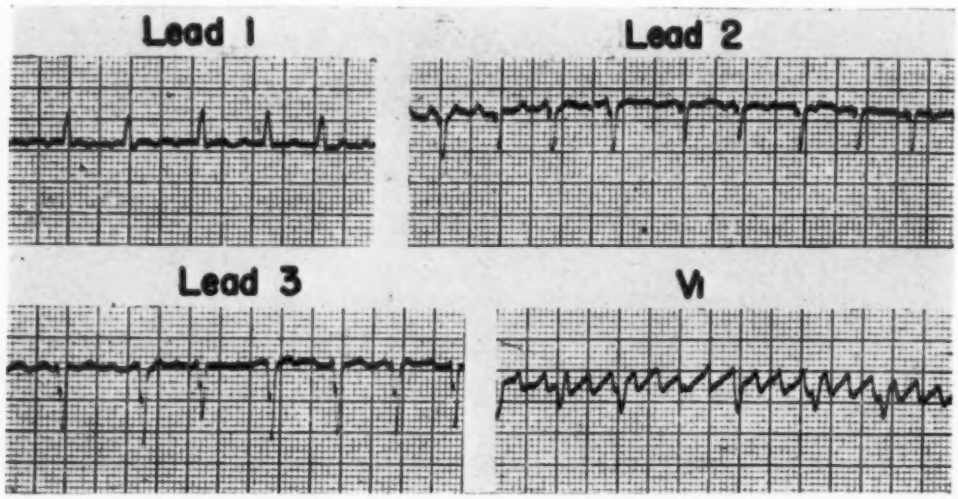

Fig. 5.—Patient Der. This shows a fast auricular rate (400 per minute), changing direction of the P waves, and isoelectric P-P intervals in Leads I to III; there are typical flutter waves in V_1 at the same rate.

In patient May (Fig. 8) auricular fibrillation, flutter, and auricular tachycardia with varying partial block occurred on different occasions. The flutter and tachycardia showed identical auricular rates. This patient also had premature auricular contractions on other occasions.

COMMENT

Prinzmetal and associates[12] demonstrated the fundamental similarity in dogs of auricular flutter and auricular tachycardia. Our material has also shown a close similarity in human subjects of the classical pattern of flutter and auricular tachycardia. Although auricular tachycardia tends to be slower than flutter, in our series a separation by this means was not possible. The rate of auricular contractions in our material was as slow as 158 per minute. Three of our patients showed auricular rates over 300 with one at 400. Three patients showed variation on different dates between flutter and tachycardia with block. Two patients showed auricular fibrillation and tachycardia with block on different

occasions. Two patients showed confusion within the same tracing, one lead suggesting tachycardia with block and another containing typical flutter waves at the same rate. Carotid sinus pressure had the same effect in both conditions.

Our material demonstrates that there is no clear differentiation between auricular flutter and auricular tachycardia with block. If the two conditions originate in a like manner, their different appearance might be explained by variations in the pathway through the auricle. Fig. 5 suggests such a possibility, showing upright and inverted P waves in the limb leads and flutter waves in V_1,

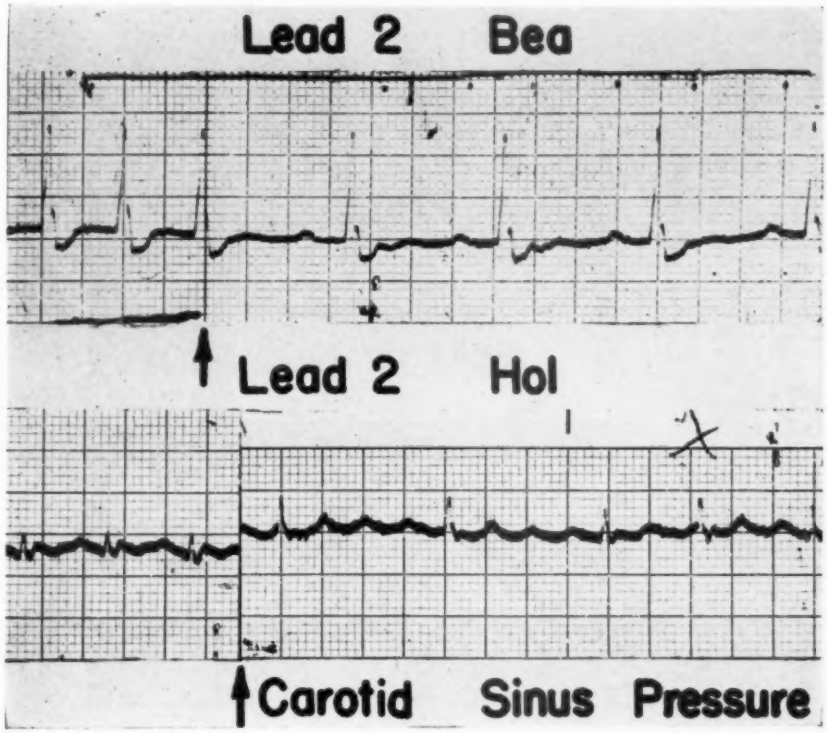

Fig. 6.—Carotid sinus pressure produced 2:1 A-V block in paroxysmal auricular tachycardia without a change of the rate (158 per minute, patient Bea, upper tracing). In a patient (Hol) with paroxysmal auricular tachycardia and 2:1 A-V block, carotid sinus pressure increased the block to 3:1 and the auricular rate from 286 to 316 per minute.

all at the same rate. A change in pathway would explain also the occurrence in patient May (Fig. 8) of the identical rate of flutter and auricular tachycardia on different days. This hypothesis is supported by Scherf,[5] who changed the direction of P waves, or flutter waves, by means of vagotomy and ligature of the intra-auricular bundle.

Nine of the ten patients reported here had heart failure. This indicates a clinical difference between ordinary paroxysmal auricular tachycardia, a relatively benign condition not usually associated with heart failure,[17] and auricular tachycardia with A-V block. Tachycardia without block is usually reported without concomitant organic heart disease.

SUMMARY

Ten patients with auricular rates from 158 to 400 per minute and various degrees of A-V block are presented. The electrocardiograms were analyzed to differentiate between auricular flutter and paroxysmal tachycardia. Using as criteria the appearance of isoelectric P-P or T-P intervals, the auricular rate, and the response to carotid sinus pressure, it was impossible to arrive at any clear-cut differentiation between these two conditions. These results are compatible with Prinzmetal's hypothesis that the mechanisms of auricular flutter and paroxysmal tachycardia are essentially the same.

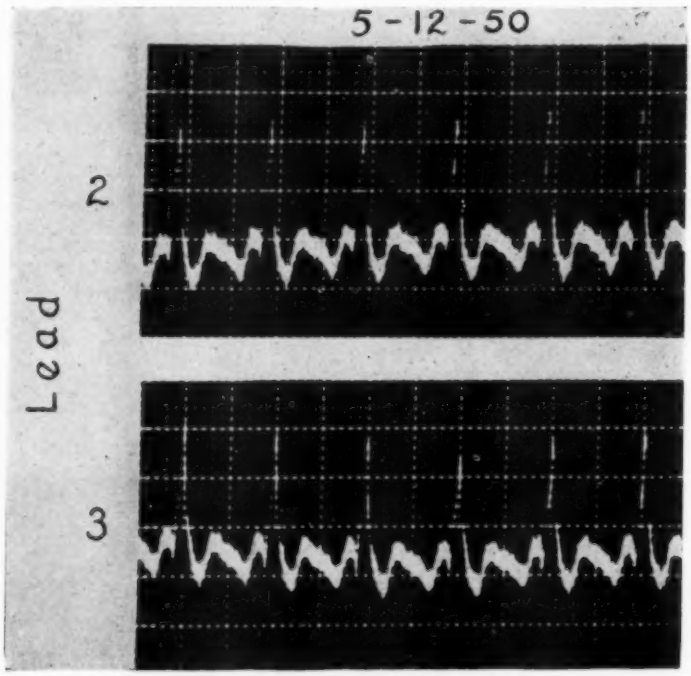

Fig. 7A.—Showing auricular flutter (rate 300 per minute) in patient Kal.

APPENDIX

CASE 1.—Hlu is a 72-year-old white janitor admitted to the hospital on Jan. 30, 1950, and discharged on March 11, 1950. He was suffering from generalized edema of five weeks' duration. He had been diagnosed as having Bright's disease in 1942. Physical examination showed a blood pressure of 196/77 mm. Hg; the pulse was 44 and regular. The heart sounds were normal. There was 2 plus edema of the abdominal wall with an enlarged liver down 5 cm. There was also 2 plus edema of the hands and forearms and 4 plus edema of the legs, thighs, and sacral region. Chest roentgenograms showed left pleural effusion masking the cardiac contour. The urine consistently showed 2 to 4 plus albumin with many casts. The hemoglobin was 9.6 Gm. per 100 c.c. The blood urea nitrogen was 40 mg. per cent. The clinical diagnosis was chronic glomerulonephritis with the nephrotic syndrome. The electrocardiogram is shown in Fig. 1.

CASE 2.—Dov is a 39-year-old, white, female secretary admitted to the hospital on Oct. 24, 1950, and discharged on Nov. 10, 1950. The complaints were palpitation of the heart for one week and pain in the right upper quadrant for about a month. She had had rheumatic fever at

the age of 12 and 15 years and had known of a heart murmur since the age of 15 years. In August, 1950, she saw a doctor because of nausea, diarrhea, and weakness. Apparently, heart failure was diagnosed because digitalis was administered and continued until the present admission. When first seen on Oct. 23, 1950, the cardiac rhythm was totally irregular. The electrocardiogram on that date showed auricular fibrillation with an irregular ventricular rate of 120 to 130 and F waves at a rate of 480.

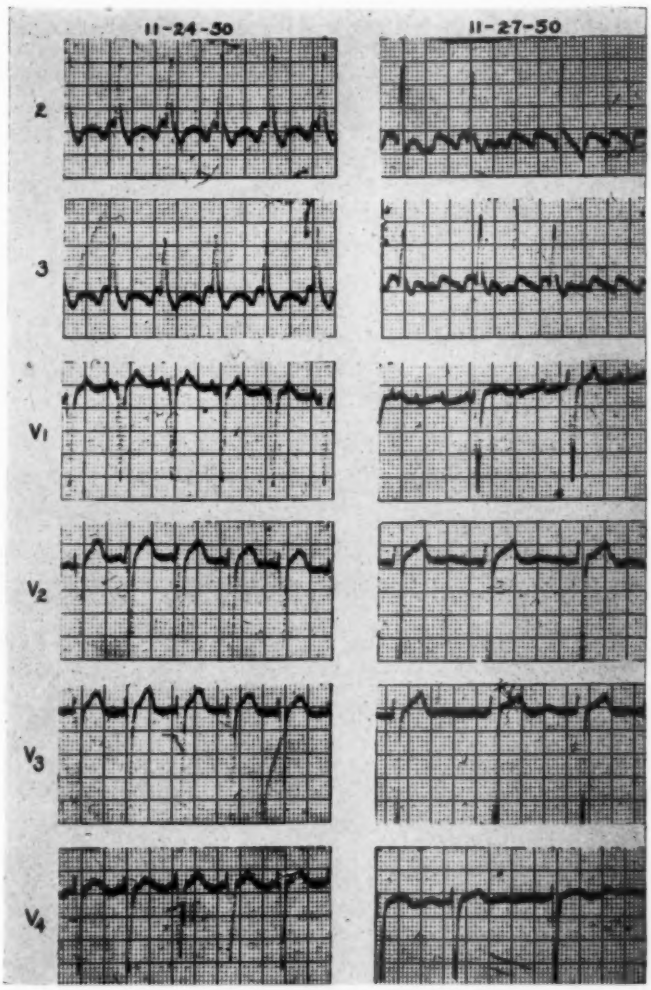

Fig. 7*B*.—There is auricular flutter at a rate of 268 per minute (Patient Kal). P-P intervals attain isoelectricity in the chest leads and approach isoelectricity in Leads II and III (Nov. 24, 1950). In the second tracing (Nov. 27, 1950), there is impure flutter (Leads II and III) at the same rate, with isoelectric P-P intervals in the chest leads.

Examination showed the patient to be in no acute distress, the only complaint being palpitation. There was no orthopnea. The lungs were clear. The heart was enlarged to the left. The blood pressure was 140/90 mm. Hg. The pulse was 106 and recorded as irregular. The first sound at the apex was accentuated; a Grade 2 systolic murmur was heard and also a low-pitched diastolic murmur characteristic of mitral stenosis. P_2 was louder than A_2. The liver was enlarged 2 cm. There was no edema. Chest roentgenograms showed a greatly enlarged heart of

mitral shape. The lung fields were clear. The diagnosis was mitral stenosis and insufficiency with heart failure. The tracing of Nov. 4, 1950, is illustrated in Fig. 2.*

CASE 3.—Mac is a 59-year-old golf course caretaker admitted to the hospital on July 15, 1949, and discharged on Aug. 23, 1949. The complaints were increasing dyspnea of two weeks' duration associated with angina pectoris. The chest pain was brought on by exertion and relieved by rest. He had episodes of black-outs on marked exertion during this period. He had had some ankle edema during the past four years. He was a moderate to heavy user of whisky. Admission examination showed some cyanosis and cervical venous engorgement. There were moist râles at the bases of the lungs. The blood pressure was 150/100 mm. Hg; the pulse was 167 and regular. The heart was enlarged to the left with good sounds and no murmurs. The liver was enlarged 2 cm. There was no edema. Urinalysis was negative. The blood urea nitrogen was 12 mg. per cent. Cephalin flocculation was 3 plus in forty-eight hours. Chest roentgenograms showed an enlarged left ventricle and severe pulmonary congestion. Circulation time with Decholin was 49 seconds, venous pressure 20 cm. of water, and vital capacity 2,690 c.c. The diagnosis was arteriosclerotic heart disease with failure.

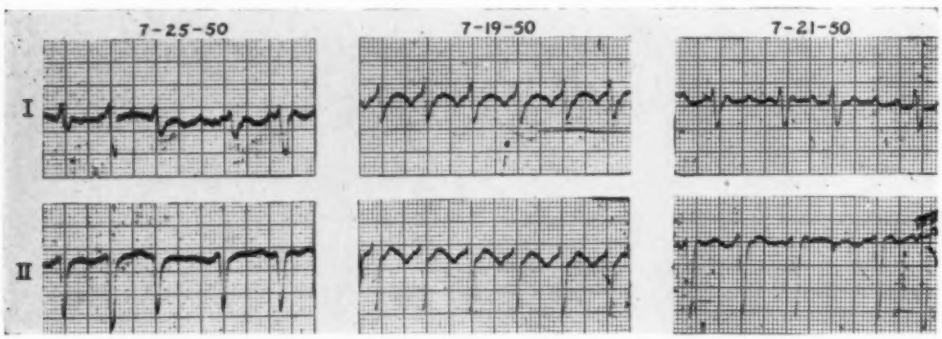

Fig. 8.—Patient May showed auricular fibrillation (July 25, 1950), auricular flutter (July 19, 1950), and auricular tachycardia with varying partial block (July 21, 1950). The auricular rates on July 19 and July 21 are the same.

The patient was given 0.4 mg. of digitoxin per day. On July 28, 1950, the rhythm changed to auricular fibrillation. The electrocardiogram is illustrated in Fig. 3.

CASE 4.—Ste was a 57-year-old butcher who was admitted to the hospital on Feb. 18, 1950, and died on March 22, 1950. The complaints were dysphagia of three months' duration, gradually progressing until in January, 1950, only liquids could be downed. A roentgenogram then showed narrowing of the esophagus. He lost 40 pounds in two months. He was a chronic alcoholic of forty years' standing. He had had a mild cough for about ten years. Examination showed him to be poorly nourished and chronically ill. There was a stony, hard nodule in the right supraclavicular space. The lungs were clear. The blood pressure was 128/80 mm. Hg. The heart was enlarged with the apex in the sixth intercostal space 10 cm. out from the sternal border. There were frequent extrasystoles. A loud friction rub was heard all over the precordium. The liver was enlarged 3 cm. The urine was negative. Roentgenograms of the esophagus showed a constriction just below the aortic arch. Biopsy of the supraclavicular node showed squamous-cell carcinoma. The diagnoses were carcinoma of the esophagus and paroxysmal auricular tachycardia with 2:1 A-V block. The electrocardiogram is illustrated in Fig. 3.

CASE 5.—Der is a 57-year-old white man admitted to the hospital on March 26, 1950, and discharged on April 27, 1950. The complaints were intermittent ankle edema for two years and nocturnal dyspnea for ten days. He had had a penile lesion fifteen years before and was treated between 1944 and 1947 for syphilis with intravenous arsenicals. One blood pressure in that period

*We wish to thank Dr. Moses Barron for permission to use this case.

was recorded at 150/110 mm. Hg. Admission examination showed slight neck vein distention and a blood pressure of 136/100 mm. Hg. The heart was enlarged to the left. There was an apical Grade 1 systolic murmur. The liver was enlarged 3 cm. Venous pressure was 17.5 cm. of saline. Decholin circulation time was 20 seconds. Chest roentgenograms showed a markedly enlarged heart with bilateral pulmonary congestion and pleural effusion. The urine was negative. The Wassermann reaction was positive. In addition to syphilis, the cardiac diagnosis was hypertensive heart disease with heart failure. The variations in the auricular rhythm are illustrated in Figs. 4 and 5.

CASE 6.—Dou is a 36-year-old labor supervisor admitted to the hospital on May 25, 1950, and discharged on July 28, 1950. The complaints were dyspnea, palpitation, orthopnea, and cough of five months' duration. He had had chorea at the age of 7 years. Examination showed the blood pressure to be 130/80 mm. Hg, temperature 102° F., and pulse 142 and irregular. There were numerous moist râles at both pulmonary bases with bronchial breathing at the left base posteriorly. The heart rhythm was totally irregular with a considerable pulse deficit. At the apex were heard loud systolic and low-pitched, rumbling diastolic murmurs characteristic of mitral stenosis. There was 2 plus edema of the ankles. Chest roentgenograms showed moderate cardiac enlargement with pulmonary edema and bilateral effusion. The white blood cell count was 13,200 with 83 per cent polymorphonuclears, 10 per cent lymphocytes, and 5 per cent monocytes. The erythrocyte sedimentation rate was 45 mm. in an hour (Westergren). The diagnoses were mitral stenosis and insufficiency in heart failure and rheumatic pneumonia. The electrocardiograms are shown in Fig. 4.

CASE 7.—Bea is a 63-year-old white man admitted to the hospital on July 16, 1950, and discharged on Oct. 3, 1950. The complaints were dyspnea and hemoptysis. He had noted some nocturnal dyspnea in 1949, and the blood pressure was found to be 212/128 mm. Hg. Following an hemoptysis then, the hemoglobin was 8.4 Gm. The dyspnea increased during the spring of 1950, and recurrence of hemoptysis led to the hospital admission. Examination showed the neck veins to be slightly distended; the heart was enlarged to the left, pulse 160 and regular, the blood pressure 180/130 mm. Hg. Carotid sinus pressure reduced the heart rate to 60 to 70. There were râles at the lung bases. The liver was down 2 cm. No edema was noted. The hemoglobin was 8.8 Gm., the blood urea nitrogen 32 mg. per cent. Chest roentgenograms showed left ventricular cardiac enlargement with pulmonary edema and some effusion bilaterally. The cardiac diagnoses were hypertensive heart disease and heart failure. The electrocardiogram is illustrated in Fig. 6.

CASE 8.—Hol, a 60-year-old bookkeeper, was admitted to the hospital on Sept. 13, 1950, and died on Oct. 28, 1950. He gave a history of increasing dyspnea and orthopnea over a period of three years. He had had a cough for a year and ankle edema for three weeks. There was no history of hypertension. Examination showed the patient to be in severe respiratory distress with pallor and cyanosis. There was distention of the neck veins. The anteroposterior diameter of the chest was widened; the breath sounds were decreased with coarse râles throughout. The blood pressure was 112/80 mm. Hg. The heart was enlarged 11 cm. to the left in the sixth intercostal space. The abdomen was tense and protuberant. There was extreme pitting edema of the legs. Venous pressure was 35 cm. of water; the circulation time (Decholin) was 12 seconds; the vital capacity was 1.6 L. The urine contained a trace of albumin. The chest roentgenogram showed diffuse cardiac enlargement. The diagnoses were pulmonary emphysema and cor pulmonale with right heart failure.

The patient was treated with digitoxin and quinidine. He reverted to normal rhythm on Sept. 28, 1950, with no improvement in the critical condition. The electrocardiogram is illustrated in Fig. 6.

CASE 9.—Kal is a 56-year-old white man who entered the hospital on Nov. 22, 1950, with the complaint of exertional dyspnea of two years' duration. The dyspnea had gradually increased, and for the preceding month the patient had had dyspnea on walking less than a block. Examination showed an extremely dyspneic, orthopneic individual with a greatly increased anteroposterior chest diameter. Chest excursion on respiration was diminished. The breath sounds

were diminished at both bases. The heart showed enlargement to the left with a loud A_2 and no murmurs. The rate was 140 and regular. The blood pressure was 150/90 mm. Hg. The urine showed 1 plus albuminuria. The vital capacity was 1.8 L. with a very slow exhalation. Chest roentgenograms showed gross cardiac enlargement and generalized emphysema. The diagnoses were chronic emphysema and cor pulmonale. Electrocardiograms are illustrated in Figs. 7*A* and 7*B*.

CASE 10.—May is an 83-year-old man admitted to the hospital on July 15, 1950, and discharged on Aug. 17, 1950. He gave a history of three months of malaise, dyspnea, orthopnea, and ankle edema. For a year he had noted chest pain brought on by exertion and relieved by nitroglycerin. He reported the diagnosis of diabetes made eleven years previously. Examination showed a blood pressure of 118/80 mm. Hg; the heart was not enlarged; there were no murmurs. Dullness, muffled breath sounds, and diminished fremitus were found over the lower one-half of both lung fields. The liver was felt 4 cm. below the costal margin. There was no edema. The urine showed a trace of albumin but no sugar. The blood urea nitrogen was 21 and the blood sugar 177 mg. per 100 c.c. Chest roentgenograms confirmed the clinical impression of bilateral pleural effusion. The patient was treated with digitoxin, Dicumarol, and diuretics. Diet alone controlled the diabetes. Digitoxin was discontinued when the abnormality of the electrocardiogram was discovered. The patient became disoriented and was transferred to the psychiatry section on Aug. 9, 1950. He left the hospital against advice with the final diagnoses of arteriosclerotic heart disease, cerebral arteriosclerosis, and diabetes mellitus. The electrocardiograms are shown in Fig. 8.

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THE ACTION OF PROCAINE AMIDE ON THE HEART

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THE quinidine-like action of procaine has been found to be of interest and of value in the control of certain cardiac arrhythmias.[1] Procaine amide hydrochloride (Pronestyl) has recently been introduced and heralded for the treatment of ventricular tachycardias. Mark and associates[2] found that it protected dogs against epinephrine-induced arrhythmias during cyclopropane anesthesia, and in man ventricular extrasystoles were suppressed by single oral doses when quinidine had been ineffective. Kinsman and co-workers[3] reported on its use in a variety of arrhythmias; ventricular tachycardias were terminated, and it was thought that the drug might be of value against supraventricular arrhythmias. Procaine amide may be administered intravenously or orally. The only unfavorable action noted has been a moderate fall in blood pressure. There is said to be absence of the toxic action on the central nervous system which limits the use of procaine in conscious patients. The present study on cold-blooded and mammalian heart muscle shows this drug to possess a well-marked depressant action, comparable to that of quinidine.

Observations have been made on the heart of the turtle *Pseudemys elegans* according to the plan followed in this laboratory to study drug action upon the fundamental properties of heart muscle. On the auricle, procaine amide in concentrations up to 1:10,000 caused only slight change in rate, rhythm, or beat size. Rhythmicity was not depressed in the auricle or spontaneously beating ventricular strips, and driven ventricular strips often showed spontaneous beats at the end of the experiment. While the auricular rate tended to quicken, such increases rarely exceeded 10 per cent, and the addition of atropine seldom caused further increase. Contraction mechanically recorded was not depressed either in the spontaneously beating auricles or the rhythmically stimulated ventricular strips. This is in contrast to quinidine which in concentration of 1:50,000 or greater usually caused reduction of beat size. Instead of the diastolic shortening seen with many cardiac drugs when given in high dosage, slight relaxation occurred. The threshold for electrical stimulation of rhythmically driven ventricular strips was significantly elevated. In general, the intensity of this action varied directly with the concentration, though there was some overlapping (Fig. 1). The latent period, the shock to the Q interval of the proximal electrogram, was little affected. The refractory period, measured by the Q-T interval of a unipolar electrogram, showed no appreciable change even with the highest concentrations.

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Fiber conduction time was increased (Fig. 2). For concentrations of 1:10,000 this effect was proportionally greater than that on threshold, but at lower concentrations the degree of action was about the same. The relation of effect to initial conduction time is illustrated by the response to a concentration of 1:50,000 in a strip with an exceptionally long conduction time. The outstanding action

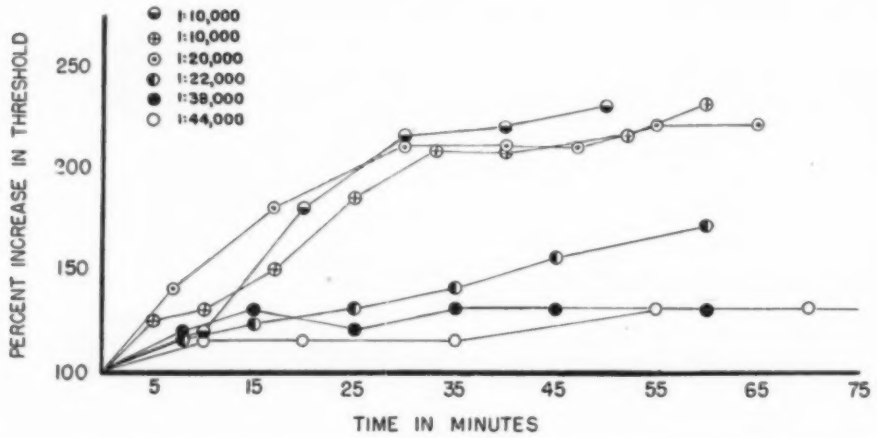

Fig. 1.—The effect of varying concentrations of procaine amide on the threshold for electrical stimulation of rhythmically stimulated strips of turtle ventricle.

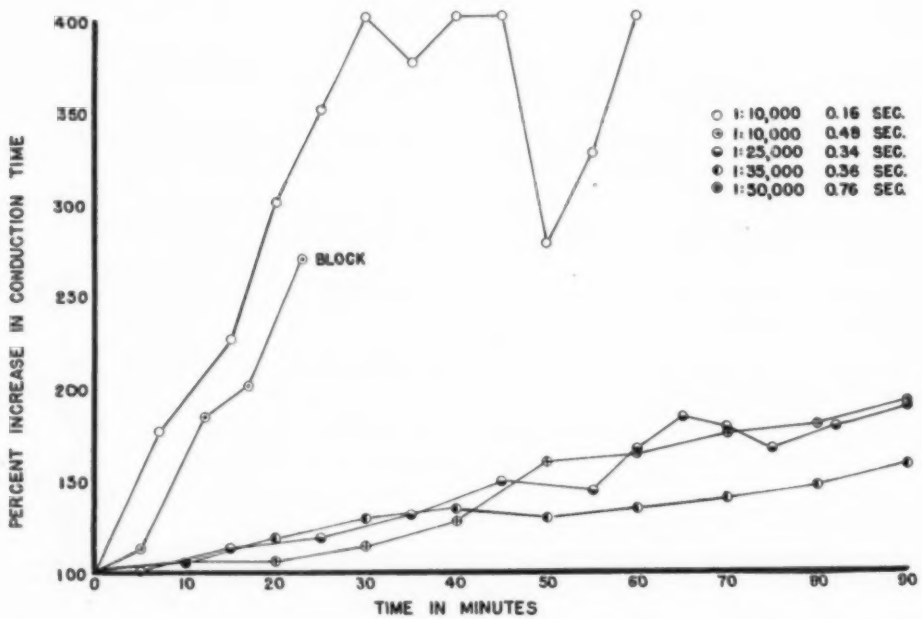

Fig. 2.—The effect of varying concentrations of procaine amide on fiber conduction time in driven strips of turtle ventricle. The initial conduction times for the interelectrode distances, usually about 12 mm., are given. The pronounced action of 1:50,000 is related to the long initial conduction time.

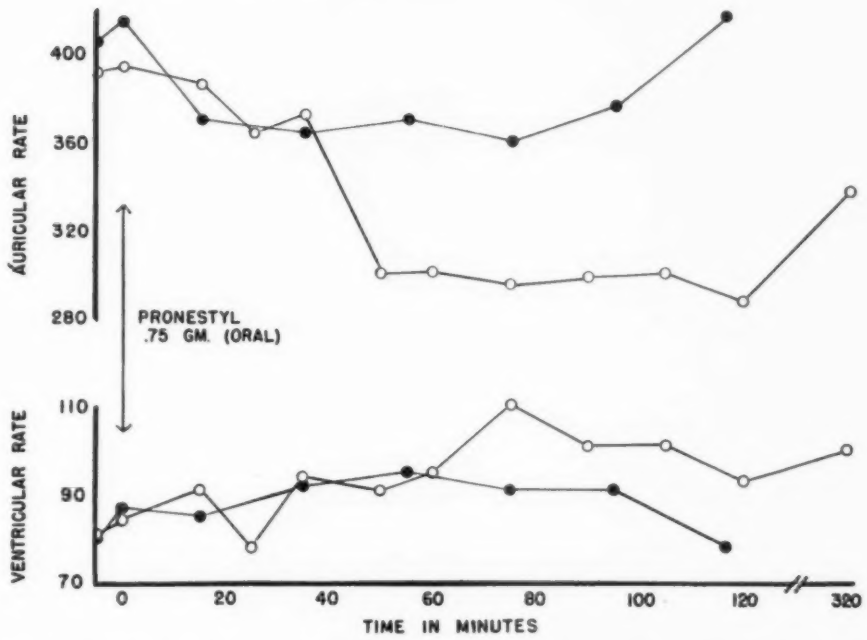

Fig. 3.—This illustrates the action of procaine amide in two cases of auricular fibrillation: solid circles, from a man aged 72 years; open circles, from a woman of 67 years. Both patients were digitalized and free from congestive failure. There was no change in blood pressure.

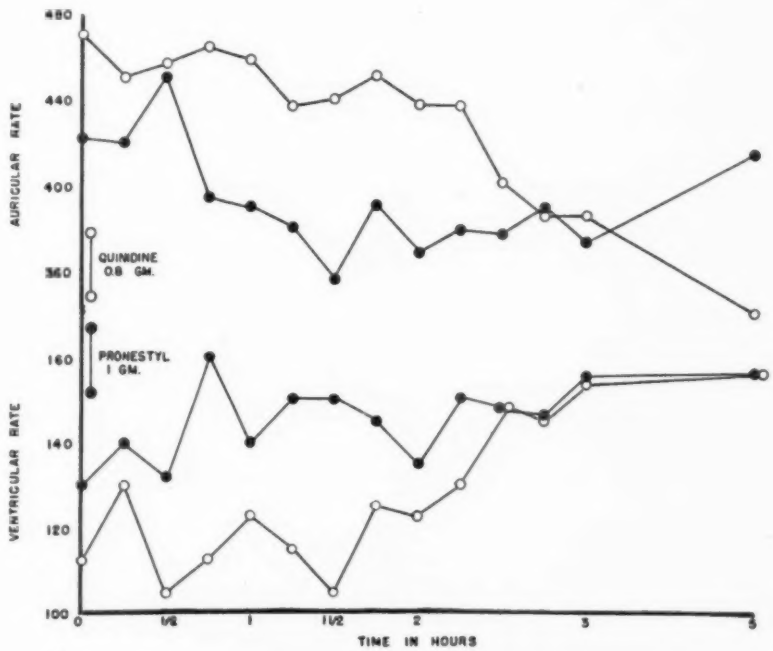

Fig. 4.—Comparison of procaine amide and quinidine in a case of mitral stenosis with fibrillation. Blood pressure was not influenced and no side actions occurred with either drug.

of the drug revealed by the reactions of the turtle heart was to raise the threshold for stimulation and consequently to depress conduction in ventricular muscle.

Observations on the action of procaine amide in man have also been made. The series, though small, illustrates the range of action that may be anticipated. In patients with normal sinus rhythm single oral doses of 0.75 and 1.0 Gm. caused no change in heart rate or P-R or QRS intervals recorded by the electrocardiogram. There was a slight fall in both systolic and diastolic blood pressures, perhaps no more than might have occurred during any two-hour period of bed rest. Gastric irritation was not encountered. In five cases of auricular fibrillation and one of flutter single oral doses of 0.75 and 1.0 Gm. caused lowering of

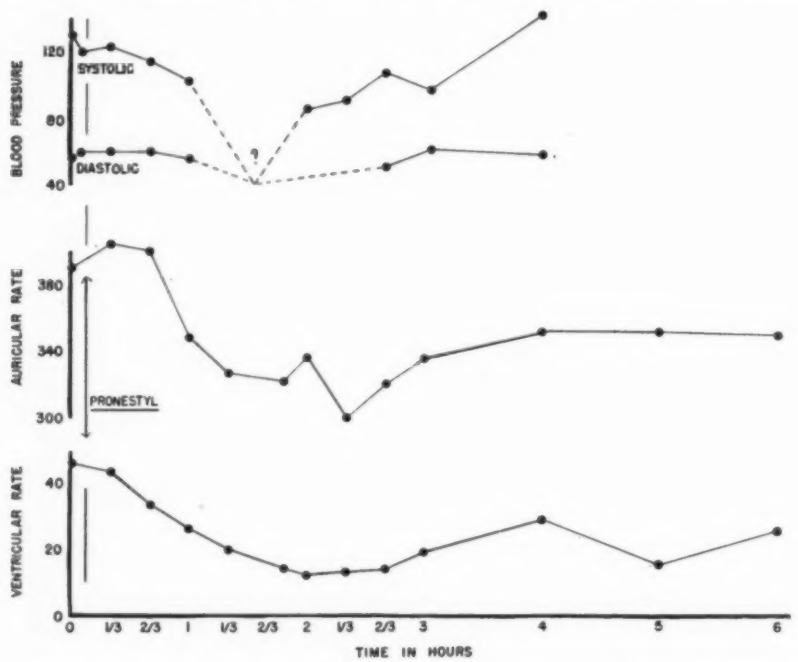

Fig. 5.—The response to 1 Gm. of procaine amide orally in a woman with auricular fibrillation and a slow ventricular rate. Auricular slowing was 25 per cent, but there was severe depression of conduction and the ventricular pacemaker.

the auricular rate from 12 to 25 per cent. In all but one there was the expected secondary rise in ventricular rate, and in this group there was no significant change in blood pressure. Variability of response is illustrated in Fig. 3. These patients were of about the same age, under digitalis, and free from congestive failure, but in one the effect was twice as great. A comparison of procaine amide and quinidine in the same patient is shown in Fig. 4. In each instance the quantity given was considered the maximal, safe, single oral dose. This and other comparative observations indicate that procaine amide is absorbed more promptly, produces its maximal effect earlier, and leaves the heart more rapidly than quinidine. The profound depressant action that this drug may cause in the region of the junctional tissues is illustrated in Figs. 5 and 6. It was not appreciated before the

drug was given that the patient had experienced syncopal attacks, presumably due to complete heart block. The effect on the auricle was no greater than that seen in other cases, but complete block, bundle branch block, and severe depression of the idioventricular pacemaker followed. Sweating was profuse, but in spite of a heart rate of 13 per minute and absence of measurable blood pressure there was no loss of consciousness, no convulsive movements or anginal pain. The appearance of bundle branch block under procaine amide has also been seen by Kinsman and associates.[3] Mention is made of an additional case of auricular

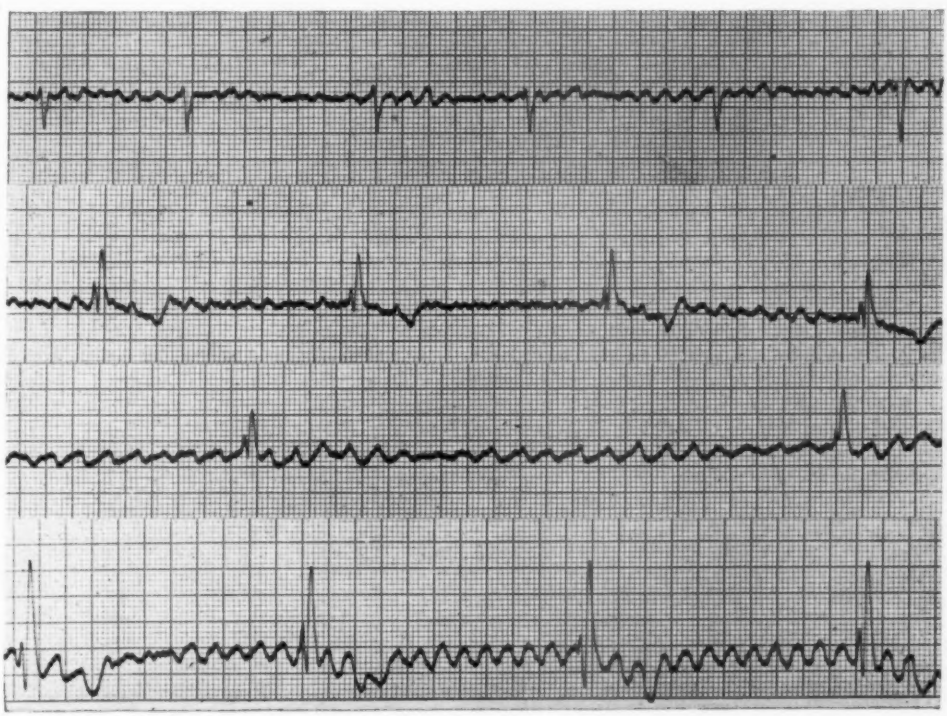

Fig. 6.—Electrocardiograms from the observation recorded in Fig. 5. Top line: initial record, ventricular rate 47; second line: 40 minutes after drug, ventricular rate 33, auricular, 400; third line: 80 minutes after drug, ventricular rate 13, auricular 300; fourth line: 4 hours after drug, ventricular rate 29, auricular 352. Bundle branch block was still present 24 hours after the drug was given.

fibrillation which appeared early in the course of acute myocardial infarction; the action on the auricle could not be determined since fibrillation waves were not measurable. After 1.0 Gm. of procaine amide fibrillation was replaced by a regular supraventricular tachycardia, and this was not influenced by further amounts. (A total of 4.0 Gm. was given in thirty hours.) Heart block appeared shortly before death.

Limited observations have been made in a few cases of ventricular tachycardia. That illustrated in Fig. 7 occurred in a patient with bacterial endocarditis. Forty minutes after 1 Gm. of procaine amide given intravenously there was a 43 per cent slowing of the ventricular rate, and twenty minutes later normal

rhythm was recorded. Other instances were seen in patients with severe myocardial infarction, but the data are incomplete. In one, 0.4 Gm. given intravenously apparently restored normal rhythm after slowing the rate from 210 to 190 per minute; fifteen minutes later, after 0.5 Gm. of the drug, ventricular tachycardia returned with a rate of 270. This was soon replaced by terminal ventricular fibrillation. A patient with auricular fibrillation developed ventricular tachycardia following severe anterior infarction. Procaine amide, 0.5 Gm. orally, caused short periods of ventricular standstill during which apparently normal auricular waves were seen. These alternated with shorter runs of ventricular tachycardia. Further amounts of the drug given orally were ineffective, and ventricular tachycardia continued until death.

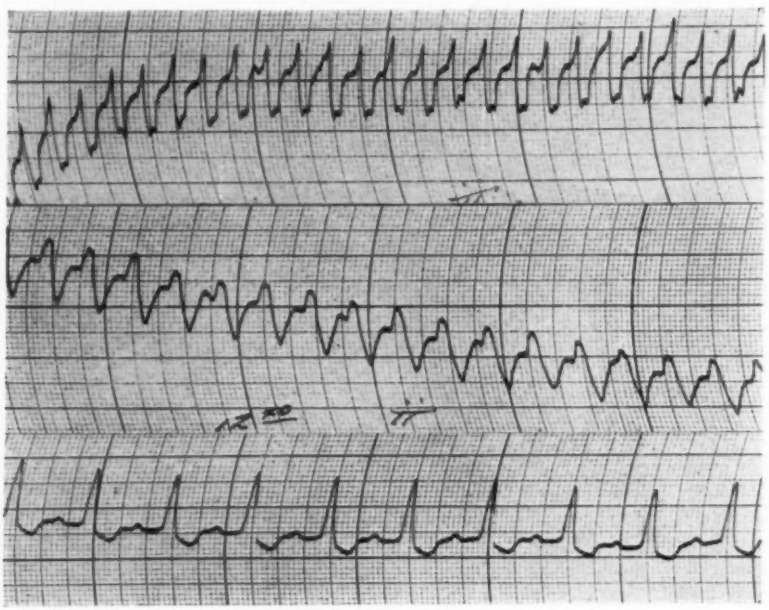

Fig. 7.—Response of ventricular tachycardia to 1.0 Gm. of procaine amide given intravenously. Top line: initial record, rate 255 per minute; middle: 40 minutes after drug, 43 per cent slowing of rate; bottom: 1 hour after beginning of injection, sinus rhythm, rate 92.

Comparative observations on the action of procaine amide and quinidine were made in a case of intermittent ventricular tachycardia that had followed myocardial infarction. The uncontrolled rate was 180 per minute; this was lowered to 123 to 130 by oral quinidine. While the patient was under quinidine 1 Gm. of procaine amide intravenously caused an additional 17 per cent slowing. A few normal beats appeared, but the tachycardia was not broken. Under similar conditions, 0.8 Gm. of quinidine gluconate intravenously caused the same degree of slowing. Twenty minutes after the injection had been completed, the man vomited, the attack stopped, and the rhythm remained normal for several hours.

SUMMARY

Procaine amide hydrochloride has been studied in the turtle heart and in man and found to have a pronounced quinidine-like action. In the cold-blooded heart its chief effect was to raise the threshold for electrical stimulation and in consequence to lengthen conduction time in ventricular muscle. In contrast to quinidine, contractility was not depressed even by high concentrations. Rhythmicity and refractory period were not altered.

In patients with normal rhythm single oral doses produced no changes. Blood pressure was not significantly influenced. Patients with auricular fibrillation showed slowing of the auricular rate ranging from 12 to 25 per cent. Comparative observations in the same patients showed that procaine amide produced its maximal effect earlier and left the heart more rapidly than quinidine. In one case the drug caused complete heart block, bundle branch block, and severe depression of the ventricular pacemaker. Experimental and clinical observations indicate that this drug may be particularly dangerous when there is disease in the junctional tissues. Instances of termination of ventricular tachycardia after previous slowing of rate were also cited.

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THE MYTH OF STRICT BED REST IN THE TREATMENT OF HEART DISEASE

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REST to the affected organ is a cardinal principle in the treatment of disease. A fractured bone is immobilized in a splint or a cast to promote healing. A lung is compressed by pneumothorax or thoracoplasty to treat an active tuberculous lesion. Likewise, physical rest, particularly in bed, is prescribed for many types of heart disease. Inasmuch as the heart cannot be placed at complete rest, it is generally thought that the maximum rest that can be given to this organ will be obtained with the patient strictly in bed twenty-four hours a day and spared any additional physical effort. It has become almost the universal practice to institute such a rigid regime in the treatment of acute coronary thrombosis and of many types of congestive heart failure. It is the purpose of this discussion to cast doubt on the validity of this concept, both from a theoretical and a practical point of view, and, in fact, to urge a contrary method of cardiac care, i.e., to keep the patient in an appropriate chair with the feet down for as much of the day as is comfortable.

Certain sick cardiac patients must have known since time immemorial that when they had difficulty in breathing at night in bed, they could obtain relief by sitting up with the feet over the edge of the bed, by getting into a chair, or even by standing upright. This is the common experience we witness in what is called paroxysmal nocturnal dyspnea. Often this condition is accompanied by acute pulmonary edema, and in many there is associated Cheyne-Stokes breathing. This generally occurs in left ventricular failure in patients suffering from hypertensive heart disease, aortic valvular disease, or coronary artery diseases. It also may develop in some cases of advanced mitral stenosis. In all these conditions there is pulmonary engorgement, probably brought on in its acute stage by a temporary imbalance between the two ventricles. The right ventricle is propelling more blood into the pulmonary circulation per minute than the left ventricle is expelling through the aorta, either as a result of an increase in the work of the right or a decrease in the work of the left ventricle. The result is a trapping of blood in the pulmonary circulation. When these events occur in bed with the body fairly horizontal, changing to a more upright position, either standing up or sitting in a chair with the feet down, decreases the return flow to the right side of the heart. This diminishes the output of the right ventricle because it cannot

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put out any more than it receives; during the subsequent minutes the decreased output of the left ventricle becomes adequate to drain the lungs of their excess volume, and a more normal state in the lungs is re-established.

Dramatic changes such as have been described above can take place in a short time. We can visualize what would happen if the right ventricle put out one drop more per beat than the left. Within one or two hours there might well be 250 to 500 c.c. of excess blood in the lungs. It is not difficult to conceive that acute pulmonary edema or marked respiratory distress would result. Such changes can take place if the mitral valve is so constricted that it will not permit a significant increase in flow per unit of time. As a result of a dream or the act of coitus or because of increased return flow from the periphery or any factor that increases the heart rate, the right ventricle, being undamaged and having no obstruction either to its inlet or outlet, will expel more blood to the lungs than can flow through the narrowed mitral valve. Similar distressing consequences will result if the valves are normal and the left ventricle is weakened and unable to keep pace with the increased output of the right ventricle. In a word, the two sides of the heart must work in unison. One cannot outdo the other for any length of time. On the other hand, if both are equally enfeebled and expel one drop or even 1 c.c. less per beat, there will be no pulmonary engorgement. In the course of time such a patient may feel weaker than normal, as the total peripheral supply of oxygen and nutrition to the body has decreased, but there will be no pulmonary congestion.

When the question of rest to the heart is considered, the inference from the above discussion is that really two organs must be taken into account, i.e., the right and the left ventricles. If one does less or more work while the other remains unchanged, difficulties may arise. It is true that in a normal individual the work of the heart is decreased while he is in bed, especially during sleep. The heart rate, the blood pressure, the basal metabolic rate, and the cardiac output are all decreased. Even if there is a temporary early increase from recumbency as a result of a shift of fluid from the tissues to the blood vessels, the normal heart will meet this demand without any difficulty or pulmonary congestion. The situation is not the same when certain forms of heart disease are present. If there is congestive failure or if there is a threat of its development, placing a patient in bed for hours at a time may *increase* the work of the right ventricle. A few simple observations made some years ago showed that twenty-four hours after certain cardiac patients went to bed, the vital capacity of the lungs decreased and the velocity of blood flow slowed.[1,2]

A more thorough study of the effect of posture on the dynamics of the circulation was carried out by Perera and Berliner.[3] They showed that in hypertensive heart failure when patients were kept recumbent for twelve to twenty-four hours, they developed hemodilution, increased blood volume, increased venous pressure, and a decrease in the vital capacity of the lungs. Similarly, McMichael and McGibbon had found a decrease in the vital capacity of the lungs of about 200 c.c. in the recumbent position.[4] All these changes are deleterious to those who are in heart failure or are threatened with heart failure. They are just the changes we try to prevent or to rectify in the treatment of heart

failure, and yet recumbency actually accentuates them or brings them on. The reason that such harmful effects do not more often result disastrously and that they have generally been overlooked is that medical treatment instituted simultaneously with strict bed rest in most cases undoes the harm thus produced. Digitalis, diuretics, and low-sodium diet gradually improve the situation so that we are entirely unaware of the early harm that may have occurred. It is only when medical therapy is inadequate that we see the patient's condition grow worse rapidly, with even a fatal outcome.

These observations throw light on some clinical experiences that many of us must have had these past decades. I recall seeing patients with hypertensive heart disease who were ambulatory and felt fairly well during the day, but who complained of nocturnal breathlessness. Examination would show some cardiac enlargement, possibly a gallop rhythm, no detectable peripheral edema or slight pitting, and either clear lungs or only a few basal râles. In former years, I would urge such a patient to go to bed. With equal emphasis he might reply that he did not want to go to bed, because it was the one place in which he was uncomfortable. With the recognized authority that physicians possess, I would insist and prevail in my contention that he must go to bed. A few days later the ankles would be smaller, but now hydrothorax would be present that required tapping. The patient might yet recover compensation after prolonged and heroic measures of therapy. In retrospect, it is evident that fluid left the peripheral tissues where it was doing very little harm and accumulated in the thorax where it increased breathlessness and threatened the life of the patient. Such harmful effects were more prevalent a few decades ago before we had mercurial diuretics, and I am certain that in some instances putting such patients to bed caused a fatal outcome that otherwise would not have occurred.

In the course of time, I gradually developed enough courage to treat patients with congestive heart failure when they first came in the hospital by keeping them in a chair most of the day and in some cases during the entire day. In some patients, especially those with massive anasarca, it was even necessary to keep them in a chair twenty-four hours a day as it was impossible for them to lie down. Patients had learned that themselves and were often forced to spend the last days or weeks of life in that position. We formerly were able to make some of them comfortable in bed by the use of sufficient morphine or other narcotics and thereby hastened their death. However, when recumbency was avoided or minimized, it quickly became apparent that many would respond to medical therapy, the dyspnea and edema would disappear, and compensation would be restored, although the patient never was subjected to the old strict bed rest regime. Except in the very extreme cases, such patients would be permitted to sleep in bed at night or to return to the bed from the chair for short periods of the day to take a nap or to obtain a change in position of the body. However, it became the practice to place 8 to 9 inch blocks under the headposts of the bed in order to encourage gravity to retain fluid in the lower rather than in the upper part of the body. In fact, there have been numerous instances of nocturnal dyspnea in which head blocks alone, apart from any change in medical therapy, made nights comfortable and permitted patients to have a peaceful night's sleep in bed.

While these concepts were being crystallized, certain clinical experiences in the care of acute coronary thrombosis were occurring that lent emphasis to their validity. Some fifteen years ago[1] I saw a patient 60-odd years of age who had had an acute coronary thrombosis three weeks before. He had grown progressively worse, so that when I saw him, his condition was desperate. He had marked respiratory distress with Cheyne-Stokes breathing, was irrational and semiconscious, and showed generalized pulmonary edema. He had been constantly in bed under an oxygen tent and had received numerous medications, such as digitalis, aminophylline, mercurial diuretics, and morphine. Because there was no peripheral edema, I remarked to the attending physician, "Is it not a pity that the edema is in the lungs and not in the legs?" Having nothing else to suggest, I advised that the patient be taken out of bed and placed in a comfortable chair with the feet down, with the hope that the fluid in the lungs might decrease and shift to the ankles. This was done, and in several hours there was striking improvement in his condition. The lungs gradually cleared, respirations became less labored, and in forty-eight hours pitting edema of the legs did appear. It is of interest that mercurial diuretics are often more effective in producing a diuresis when patients have peripheral pitting edema than when they have pulmonary edema. This proved to be so here, for when mercury was administered intramuscularly several days later there was a good response. This patient eventually made a satisfactory recovery. He was ambulatory and in good condition a few years later. This is a striking instance in which a patient's life appeared to have been saved entirely as a result of placing him from a bed into a chair with the feet down.

A similar and even more impressive experience took place only a few years ago. This 57-year-old man had also had an acute coronary thrombosis a week before. He developed increasing dyspnea, pulmonary edema, paroxysms of auricular fibrillation, and troublesome constant hiccup, and he became irrational. He had been seen by several outstanding cardiologists but steadily grew worse. He had received Dicumarol as an anticoagulant, quinidine because of recurrent auricular fibrillation, digitalis for left ventricular failure, frequent injections of narcotics for the marked restlessness, and oxygen for the breathlessness. When I saw him, the clinical picture was most distressing, particularly because of the annoying hiccups, the marked breathlessness, and the uncontrollable restlessness. There was obviously little to be gained from medication, as most of the drugs customarily employed had already been used. It was possible that the various medications had harmed rather than helped matters. The only advice I gave was to stop all medication, including oxygen, and to put the patient in a comfortable chair with the feet down. In ten hours, a most amazing improvement occurred. He was clear mentally, breathing was comfortable, the generalized pulmonary edema was gone, and the hiccup, though still present, was less violent and much better tolerated in this new position. The physician and nurses in charge and the family all described the events as a miracle. Here again, the only change in treatment that could account for the recovery was getting the patient out of bed and placing him in a chair. When the physician in charge, who was seeing the patient constantly, was asked whether the extraordinary improvement

could have been due to omitting all the various drugs that were being given, he replied that the dramatic change for the better occurred too rapidly to be accounted for in that way. Here, therefore, is another instance in which strict bed care was leading to a lethal outcome and life was saved by the use of the chair.

One could go on at great length citing other similar experiences. I have seen instances in which the mental state and distressing hiccup apart from breathlessness quickly improved after placing the patient in a chair. It is reasonable to assume that if a change in posture can produce such beneficial effects once these severe symptoms develop, the same complications might have been prevented if the patient had been kept in the proper position throughout the illness. This general type of reasoning has gradually led us to treat acute coronary thrombosis by keeping the patient in a chair. The purpose is still to rest the heart as much as possible and to prevent pulmonary congestion and other complications that might result from recumbency.

It is now our practice to keep a patient with an acute coronary thrombosis in a chair, beginning as early in the illness as possible. Generally, the acute pain subsides in several hours or within one day, following the use of appropriate narcotics or sedatives. Directly after this and in some instances before the pain has entirely disappeared, the chair treatment is started. The patient should be helped into the chair and later back to bed. He is to be as quiet and inactive in the chair as he would have been in bed. He may be fed by a nurse or an attendant if circumstances permit this help, but in many mild cases this is not necessary. He uses a near-by commode for bowel purposes and a bottle for urination. When a patient is treated at home and the general condition seems sufficiently good, especially if the economic circumstances do not permit the attendance of nurses, he may be allowed to take a few steps to the bathroom for bowel movements. The length of time spent in the chair may vary. Some will prefer to stay there all day, while others will want to return to bed after a few hours. In general, it appears that the longer the time spent in the chair the better. If the pain has gone and he feels comfortable, it will not be as easy to judge, either for the patient or the physician, whether he is better in the chair or the bed. Even then, many will volunteer that they are better out of bed than in bed. If there are symptoms, especially if there is any degree of breathlessness, then the advantages of the chair will become apparent quickly. The patient will almost always insist that he feels better in the chair.

The only exception, and the main contraindication, to this method of treatment is the presence of significant shock. If the patient is unconscious or in profound shock (forward or peripheral heart failure), it is obviously unwise or impossible to use the chair treatment. Blood flow to the brain would be further decreased by the upright position of the body. In that case, recumbency is preferable until the state of shock has been rectified. Thereafter, the chair treatment might yet prove advantageous. However, there are frequent instances in which shock is absent and yet cerebral symptoms such as delirium or irrational state are present where the chair treatment has proved very valuable.

Apart from the physical effects which have been discussed that result from this method of treatment, there are striking psychic advantages to be gained by

the use of the chair treatment of acute coronary thrombosis. There is something ominous and foreboding in the mind of the average patient when told to stay absolutely quiet in bed for a month or so. He quickly develops great fear that something terrible is going on or that he might suddenly die if he makes the slightest effort or movement. The difference in the psychological state of the patient is readily seen in those who had had a previous attack and were treated by the strict bed rest regime. They immediately remark how much happier and less fearsome they were on the chair method of treatment. Nowadays, when the importance of the alarm reaction is being stressed, this factor in treatment gains greater reality.

There is a further advantage in the chair treatment of coronary thrombosis when the problem of convalescence and rehabilitation comes up. It has been our custom to continue this regimen of rest in a chair for about three to four weeks. Thereafter, if progress has been satisfactory, the patient is allowed to take steps and his activities are gradually increased. When this change is instituted after a period of several weeks of absolute and strict bed rest, the patient finds himself very weak, and convalescence is often slow. Many remain feeble for weeks and some for months. There is often both mental and physical asthenia that frequently continues to be the sole incapacitating complaint. It is a not uncommon experience that patients recover from the physical injury to the heart satisfactorily and yet remain incapacitated by these neurasthenic symptoms indefinitely. It is more than likely that the chair treatment will help to lessen the likelihood of such eventualities, for the patients have been in better spirits and find themselves much less physically debilitated when they start increasing the scope of their activities.

It would be hardly necessary to employ the chair method of treatment in acute coronary thrombosis or for that matter in any case of congestive heart failure if the advantages of posture could be obtained in a bed. The ordinary hospital bed in which the back can be raised is not an adequate substitute. The feet are still at the same level as the hips. There are so-called cardiac beds that can be cranked into positions that simulate a chair. In general, they do not work as well. The back cannot be kept almost horizontal and the mattress at the knees does not bend easily enough to attain the comfortable position for the legs that is obtained with an average broad-arm chair. Although it is conceivable that a proper bed or "bed-chair" may be constructed that will serve this purpose and will obviate the transport of the patient from bed to chair, at present it seems necessary to employ a comfortable sturdy chair, preferably with arm rests and foot rests. In patients' homes, the physician can quickly tell which chair will be most suitable for the patient by sitting in it himself and seeing if he finds it comfortable.

Apart from the chair treatment, all the other methods that are customarily employed in the care of coronary patients are used, i.e., oxygen, anticoagulants, and so forth. As of the present, seventy patients with acute coronary thrombosis have been treated in this way. It is impossible to draw conclusions from comparative statistics. Our cases have been artificially selected. They have not been absolutely alternate cases or consecutive cases. In some instances, the

patient's family or the attending physician refused to accept the suggestion that the patient should be put in a chair. The principle of strict bed rest in the treatment of coronary thrombosis has been so engrained in the minds of the lay public and the medical profession that it is difficult to make such a drastic change. There is a prevailing opinion that if a cardiac patient dies in bed all is forgiven, but if he dies out of bed the physician in charge fears that he might be blamed for the fatal outcome. Furthermore, patients who were in shock or unconscious would not be put in a chair and therefore would not appear in this series. Finally, the variations in the course and outcome of acute coronary thrombosis are so great that it will require large numbers of cases to establish incontrovertible evidence in favor of or against any new method of treatment. It can be stated, however, that during this study there was a period when twenty consecutive patients entering one of our wards were subjected to this method of therapy with only one death.

Of seventy patients who underwent the chair treatment for coronary thrombosis, there were only seven deaths.[5] All patients began the chair treatment some time during the first week. Some were seen for the first time several days after the onset of the illness. Others were in considerable pain and had had varying degrees of shock for one to several days and only then began chair treatment. That these patients included many who appeared to be critically ill is illustrated by the fact that when chair treatment began, many had fever, and some had a pericardial friction rub, complete heart block, pulmonary edema, or any of the features customarily seen in this disease. The development of acute pulmonary edema or dyspnea not already present or the aggravation of such states was extremely rare after chair treatment was begun. The entire experience has left nothing but a favorable and optimistic impression on the physician and nurses in attendance.

The immediate mortality of about 10 per cent is low enough to encourage us in the belief that this method of treatment does not carry with it any risk. In fact, it would appear that the immediate mortality might actually be lessened. One might be fearful that the tendency of the ventricle to rupture might be enhanced with this mode of treatment. If this were true, sudden death during the first week or two should occur more frequently than is customarily seen, for perforations take place almost invariably during the early days of infarction. This has occurred in only one case. As was stated above, comparisons with other figures are difficult to make. However, in recent years at the Peter Bent Brigham Hospital, where most of these cases have been treated, the expected mortality of acute coronary thrombosis under Dicumarol and strict bed rest treatment has been 15 per cent, which is greater than in the group treated in a chair.

Apart from the question of immediate mortality, the chair treatment has lightened the burden of the care of the patient. The nurses in the hospital find it easier to look after the patients, and, if the illness is treated at home, the household is less disturbed. Furthermore, with male patients there has been less difficulty as far as bladder function is concerned. It has rarely been necessary to use a catheter or to worry about urinary retention. It is also likely that with this posture we are less likely to see hypostatic or bronchopneumonia develop. Fi-

nally, although the series is too small to permit any accurate generalizations, it is not fanciful to believe that the tendency to thrombophlebitis with its danger of pulmonary embolism will be lessened.

One may ask whether the long-range effects will be different in patients treated by this method. If the left ventricle has had less work to do during the weeks in a chair, as is claimed here, than would have occurred in bed, there is no reason to believe that repair of the heart muscle will be any worse. Recovery might possibly be better. If the contrary is true, we may expect to find a greater number of instances of ventricular aneurysms or congestive heart failure coming in the wake of coronary thrombosis. As yet, it is too early to answer these questions. So far, there is no evidence of such eventualities.

SUMMARY

There is both clinical and physiological evidence to support the view that strict bed rest is deleterious to patients with congestive heart failure. There is abundant reason to believe that if heart failure is present, the heart obtains more rest with the patient in a chair with the feet down than while the patient is recumbent in bed, even if the head and back are elevated.

On the basis of this simple concept it is advised that most patients with threatened or evident congestive heart failure be treated, not in bed, but in a comfortable chair and, when they do go to bed at night to sleep, 8 to 9 inch blocks be placed under the headposts to encourage gravity to keep body fluids in the legs rather than in the lungs.

This principle has also been applied in the treatment of acute coronary thrombosis. We report a mortality of 10 per cent in the care of seventy patients with acute coronary thrombosis who were placed in chairs for varying and increasing periods of the day beginning not later than the first week of the attack. The results of this method of treatment seem encouraging and appear to have both physical and psychic advantages over the strict bed rest method of treatment.

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THE CURE OF A PATIENT WITH A VERY RESISTANT STREPTOCOCCUS VIRIDANS ENDOCARDITIS WITH MASSIVE PENICILLIN THERAPY (AVERAGE DAILY DOSE OF EIGHTY-SIX MILLION UNITS)

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THE effectiveness of penicillin in the treatment of nonhemolytic streptococcal endocarditis is well established. In most cases of subacute endocarditis, cure can be accomplished with conventional doses of penicillin, but now and then it is necessary to administer heroic doses. A review of reported treatment failures due to relapse or continued infection makes it quite clear that many such patients have not been given adequate daily doses of penicillin. If the circulating blood is not promptly sterilized or if relapse occurs subsequent to completion of a course of penicillin, it has been advised that the daily dose of penicillin should be drastically increased five- to tenfold; then the arrest of the infection would probably more nearly approach 100 per cent.[1]

More than 90 per cent of the strains of nonhemolytic streptococcus are completely inhibited in vitro by 0.1 unit or less of penicillin per milliliter[2] and are classified as the sensitive group.[1] The moderately to very resistant group requires for inhibition of growth in vitro 0.5 to 10 units or more of penicillin per milliliter. The moderately sensitive group is inhibited by penicillin in vitro in amounts which are between the above two ranges. It has been recommended that patients infected with an organism which requires 1 unit of penicillin per milliliter for in vitro inhibition should receive a daily dose of at least 5,000,000 units of penicillin.[1]

The purpose of this communication is to report a case of subacute bacterial endocarditis in which the patient was infected with a very resistant strain of *Streptococcus viridans* treated with an average daily dose of approximately 86,000,000 units of penicillin for a period of twenty-eight days.

CASE REPORT

The patient was a 33-year-old white woman, a housewife, who was first admitted to Emory University Hospital on Sept. 28, 1949.

At the age of 8 years, the patient had had severe joint pains of one month's duration. In June, 1948, she began to feel weak and then had the onset of chills, fever, sweats, and migratory joint pains involving the wrist and ankles. Areas of hemorrhage beneath the fingernails and tenderness of the finger tips were noted by the patient, and she was told by her physician at this time that she had a "leaking heart" and an "enlarged spleen." For approximately twenty-eight days

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at home, she received 600,000 units of procaine penicillin G intramuscularly daily, but the symptoms continued. Following this, she was admitted to a nearby hospital, and a *Str. viridans* was isolated from the blood. She was given thirteen transfusions and received the antibiotic therapy as listed (Table I). Relapse immediately followed the first two courses (Table I).

TABLE I. PREVIOUS ANTIBIOTIC THERAPY

ANTIBIOTIC	DATE	AMOUNT AND DURATION
1. Penicillin with carinamide (4 Gm. every 3 hours orally)	July 10 to Aug. 13, 1948	500,000 units I. M. every 3 hours for 33 days
2. Penicillin	Aug. 19 to Oct. 11, 1948	250,000 units I. M. every 3 hours for 54 days
Streptomycin	Sept. 15 to Oct. 6, 1948	1 Gm. I. M. every 6 hours for 22 days*
3. Penicillin	Oct. 11, 1948	500,000 units I. M. every 3 hours for 1 day
	Oct. 12 to Nov. 8, 1948	1,000,000 units I. M. every 3 hours for 28 days
4. Penicillin	March 15 to April 26, 1949	2,500,000 units I. M. every 3 hours for 42 days
Dihydrostreptomycin	March 23 to March 30, 1949	0.5 Gm. I. M. every 12 hours for 7 days*

*Omitted because of severe dizziness, nausea, and vomiting.

Following the third course (Table I), the patient felt improved but continued to note weakness and malaise. In March, 1949, she noted petechiae and the onset of fever and joint pains. She was readmitted to the same hospital and shortly thereafter became comatose and remained in that state for about two weeks. On regaining consciousness, she had a weakness of the right side of the face and right extremities, but this cleared in a few weeks. During this hospital admission she received the fourth course of antibiotic therapy as listed (Table I).

Following this therapy, the patient again felt improved. About June 1, 1949, she again relapsed. She was treated at home with 3,000,000 units of procaine penicillin G intramuscularly twice a week, and this was continued until September 23.

The patient was first admitted to Emory University Hospital on Sept. 28, 1949, under the care of the author. She appeared chronically ill, pale, and undernourished. There were no embolic manifestations. The heart was not enlarged. At the apex, there was a low-pitched, rumbling, mid-diastolic murmur, and over the entire precordium, but loudest at the apex, a harsh systolic murmur was audible. The spleen was palpable at the costal margin.

The urine contained no albumin, pus, or red blood cells. There was a moderate hypochromic anemia. Sedimentation rate and leucocyte and differential counts were normal. Repeated blood cultures were negative. Fluoroscopy of the heart revealed a minimal left atrial enlargement and a prominence of the pulmonary conus segment. The electrocardiogram was within normal limits. Roentgenogram of the teeth revealed an apical abscess of the right upper first molar. Crystalline penicillin intramuscularly (100,000 units every three hours) was begun on Oct. 3, 1949, and the tooth was extracted under local anesthesia on October 4. The penicillin was continued until October 8. Culture of the apical abscess grew a *Str. viridans* which growth was inhibited in vitro by 0.03 units of penicillin per milliliter. The patient was discharged on October 8 and remained free of symptoms until October 22 when she noted petechiae on the dorsum of the right hand, right knee, and hemorrhages under the nails.

She was readmitted on October 24. Physical examination revealed numerous petechiae. Otherwise, the findings were as previously described. She was afebrile. The urine was negative for albumin, and there was no microscopic hematuria. The Westergren sedimentation rate was 60

mm. in one hour. Moderate hypochromic anemia was present. The fasting total eosinophile count was 50 per cubic millimeter. Blood cultures were taken every day. These did not at first yield evidence of bacteremia, but two of four blood cultures obtained on November 2 gave a growth of *Str. viridans*. The sensitivity of this organism is shown in Table II.

TABLE II. SENSITIVITY OF THE STREPTOCOCCUS VIRIDANS

	GROWTH	NO GROWTH
Penicillin	10 U. per ml.	20 U. per ml.
Streptomycin	16 U. per ml.	50 U. per ml.
Aureomycin*	50 μg per ml.	
Chloramphenicol	50 μg per ml.	

*Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

The temperature remained normal until November 18, and at this time the patient developed chills and fever, a swollen, red, painful, distal phalanx of the left index finger, and arthralgia of the right ankle. The streptococcus was again isolated from all cultures, and its sensitivity was the same (Table II). The urine was negative for albumin but contained red blood cells. The sedimentation rate was further depressed.

Massive penicillin therapy was begun on November 22 (Fig. 1) and continued for twenty-eight days. The patient was discharged from the hospital on Dec. 22, 1949, and was followed monthly for the next twelve months. The spleen was no longer palpable. She felt well except for episodes of menorrhagia and one attack of salpingitis and has been able to carry out the duties of a housewife. Many blood cultures have been taken, all being negative. The cardiac findings remain as described, and she appears to have normal cardiac reserve.

Massive Penicillin Therapy—Methods of Administration and Observations.—For the first two days of penicillin therapy, the patient received 5,000,000 units of crystalline penicillin G sodium dissolved in 6 ml. of distilled water intramuscularly every two hours, and for the next six days 10,000,000 units of the same penicillin dissolved in 11 to 12 ml. of distilled water intramuscularly every two hours (Fig. 1). This was given deep into the outer muscles of the buttocks and upper anterior and lateral thigh muscles with the sites of injections being varied. Carinamide was attempted both by mouth and by indwelling Levine tube, but because of severe nausea and vomiting, it had to be discontinued on the second day of therapy. The nausea and vomiting subsided promptly thereafter.

By the fifth day of intramuscular penicillin, erythema, induration, and tenderness of the buttocks and thighs became marked, and by the eighth day the edema, redness, and induration extended into the sacral and lower lumbar area. The buttocks were hot and very painful. On the right buttock and upper one-third of the right thigh at sites of injections there appeared four areas of vesiculation which subsequently became black eschars. On the ninth day, because of the marked reaction, penicillin was begun intravenously (Fig. 1). On the ninth and tenth days, the patient received 10,000,000 units of crystalline penicillin G potassium† dissolved in 250 ml. of 5 per cent glucose in distilled water intravenously every six hours. On the eleventh day this was increased to 20,000,000 units of the same penicillin dissolved in 250 ml. of 5 per cent glucose in distilled water with 2 ml. of 2 per cent Novocain intravenously every 6 hours, and this was continued until the twenty-sixth day. The patient experienced burning pain along the course of the vein with each infusion, and eventually all superficial veins had become thrombosed, so that the intramuscular route had again to be utilized for the last two days of therapy (Fig. 1). Ten to twenty million units of crystalline penicillin G potassium were dissolved in 12 to 22 ml. of distilled water,

†This penicillin was 100 per cent pure penicillin G and was free of any impurities. However, 4.5 per cent sodium citrate (U.S.P.) was added as a buffering agent. The penicillin had a potency of 1,570 units per milligram. (Bristol Laboratories, Inc., Syracuse, N. Y.)

respectively. Five hundred viscosity units of hyaluronidase were dissolved in 1 ml. of distilled water and were injected first intramuscularly in the site of proposed penicillin injection. Swelling and tenderness appeared at the sites of intramuscular penicillin injections, but these reactions seemed of less intensity than observed initially and all areas resolved. On the seventh day of massive penicillin therapy, stomatitis, cheilitis, and glossitis became evident but responded in several days to parenteral vitamin B complex.

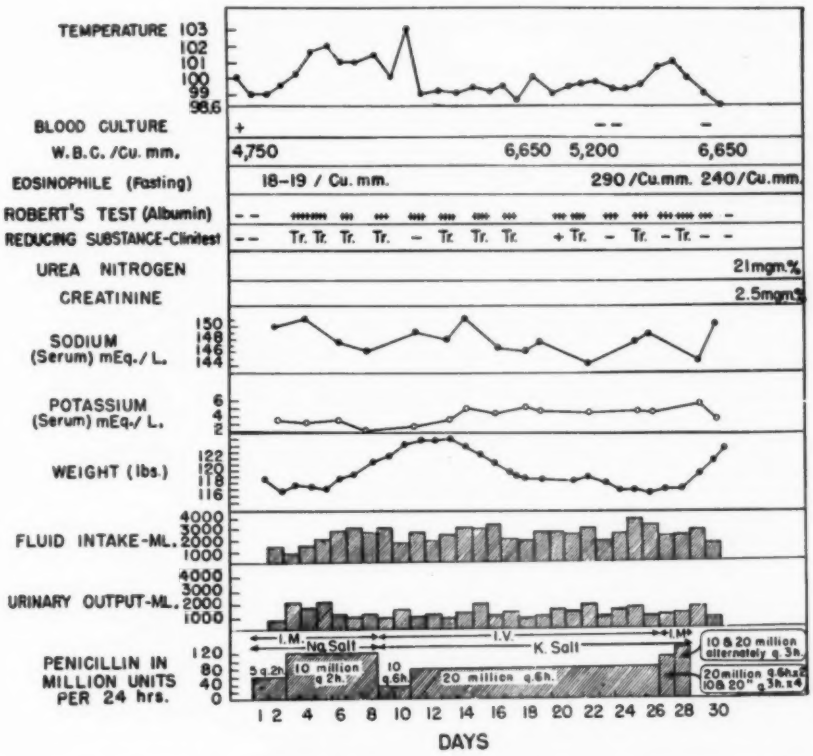

Fig. 1. –Chart showing observations and dosages of penicillin. The negative blood cultures were cultures treated with penicillinase. The positive Roberts tests for albumin in the urine were false positive, and the reducing substance was not glucose (see text) (Clinitest, Ames Company, Inc., Elkhart, Ind.). The serum sodium and potassium were determined by the Perkin Elmer internal standard flame photometer.

The patient's temperature rose to a peak elevation of 103° F. two days after cessation of the initial intramuscular method of administration (Fig. 1). It was felt that the described local reactions accounted for this elevation. During the intravenous route, the highest elevation was 100° F. When the intramuscular route was resumed, there was a rise in temperature to 101° F. with a prompt fall to normal two days after cessation of therapy. Fluctuant abscesses surrounded by induration were present in the left and right buttocks by the twenty-fifth day of therapy, and by aspiration, 115 ml. and 12 ml. of thin, dark, greasy, brown sterile fluid were obtained, respectively. The abscess of the right buttock resolved, but due to formation of a draining sinus tract and a multilocular cavity, the abscess of the left buttock was incised and drained. This resulted in prompt healing. The eschars of the left buttock healed. However, at the site of the 4 by 5 cm. eschar on the right thigh, a deep ulcer developed with a base of unhealthy fatty tissue and connective tissue. This ulcer showed no gross evidence of granulation tissue or of healing, and the area was excised and closed with normal healing.

Urinary tests (Fig. 1) for protein and for reducing substances were positive throughout the period of massive penicillin therapy. It is thought that these were false positive reactions due to the presence of penicillin.[3]

The serum potassium was low initially (Fig. 1). The patient had no subjective symptoms of potassium deficiency, nor were there any cardiac symptoms. The initial eosinophile count was low, indicating increased adrenal cortical activity which could account for the lowered serum potassium. The serum potassium returned to normal on the thirteenth day of therapy, the fifth day of administration of the potassium salt of penicillin. The serum sodium was high at first and had no relationship to the salt of penicillin administered (Fig. 1).

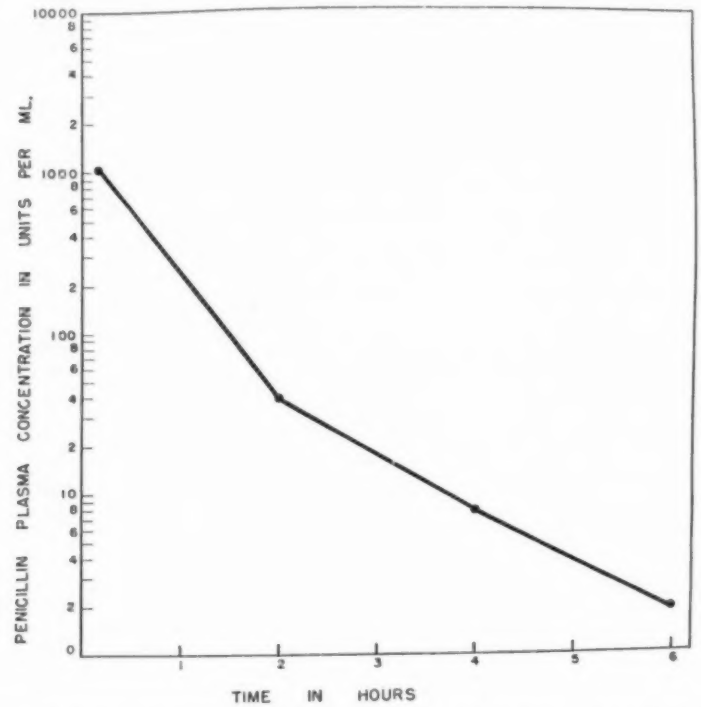

Fig. 2.—Penicillin plasma concentrations, charted on semilogarithmic scale 4 by 10 cycles, obtained after intravenous infusion of 20,000,000 units of penicillin in 250 ml. of normal saline solution every six hours for a twenty-four-hour period. Each infusion was given in approximately ten to fifteen minutes. Blood samples were taken after the termination of the last infusion.

The fluctuation in the weight (Fig. 1) of the patient can only be related to the patient's intake of food. Even though the buttocks were painful and temperature elevated during the period of intramuscular penicillin, the sense of well-being and appetite improved after the first two days. By the fourteenth day of therapy she became tired and lost her appetite. After penicillin was stopped, the appetite and mental state markedly improved, and there was a rapid increase in weight.

During the course of penicillin therapy, accurate penicillin plasma levels were not obtainable because of technical difficulties. In order to determine the penicillin plasma concentrations reached during the daily dose of 80,000,000 units of penicillin intravenously, a patient with normal renal function was given 20,000,000 units of crystalline penicillin G sodium in 250 ml. of normal saline solution intravenously every six hours for a twenty-four-hour period. Each infusion was given in approximately ten to fifteen minutes, which was the usual time required for the infusions given to the patient treated with massive doses. Samples of blood were obtained ten minutes,

two hours, four hours, and six hours after termination of the last infusion, and penicillin plasma concentrations* of 1,050 units, 39.9 units, 8.4 units, and 2 units were obtained, respectively (Fig. 2).

DISCUSSION

Tremendous doses of penicillin can be given to a patient without danger, and it appears from this patient that the only deleterious effects were local irritation and inflammation and the discomfort from the concentrated solutions. In studies of the occurrence of false positive tests in the urine for albumin and glucose during the course of massive penicillin therapy when similar doses were administered for twenty-four-hour periods,[3] no venous thromboses occurred, and only minimal discomfort along the course of the infused veins was noted by the patient. It has been suggested previously that the maximum dose of penicillin which man can tolerate is about 20,000,000 units daily.[4] It may be argued that the therapy was unnecessarily intensive, but arrest and cure of the infection resulted, and it will be in this manner that the cure of the infection will more nearly approach 100 per cent.

During the last twenty days of therapy, 100 per cent pure crystalline penicillin G potassium was utilized. The maximum tolerated daily doses of penicillin are unknown. It is likely that dosages larger than these can be tolerated by man. In 80,000,000 units of crystalline penicillin G potassium there are approximately 5.28 Gm. of potassium,† and it is possible that the toxic reactions would depend more upon the amount of potassium ion than upon the penicillin portion of the molecule. This might also apply to the sodium salt of penicillin.

It can be assumed that for sixteen days, when the patient received 20,000,000 units of penicillin intravenously every six hours, for at least two hours after each infusion, the plasma concentration of penicillin (Fig. 2) was two or more times the in vitro sensitivity (Table II). These repeated intermittent elevations of the penicillin plasma levels are sufficient for cure,[5] and it is possible that sixteen days of such therapy would have resulted in a cure. The intravenous route is the method of choice for the administration of the massive doses, and it is believed that even larger doses than those utilized in this patient could be used.

CONCLUSIONS

1. Cure of a patient with a highly resistant strain of *Str. viridans* endocarditis treated with an average daily dose of 86 million units of penicillin for twenty-eight days is reported. Previous treatment with conventional doses of penicillin and combined therapy with penicillin and streptomycin had been unsuccessful.

2. There were no deleterious effects except local reactions resulting from the injections.

*The penicillin assays were determined by Dr. William P. Boger, Hospital of the University of Pennsylvania, Philadelphia, Pa.

†Bristol Laboratories, Inc., Syracuse, N. Y.

The author expresses his appreciation to Dr. William P. Boger who did the biologic assays for penicillin in this study and also the house officers, nursing staff, and laboratory personnel of Emory University Hospital who helped make the treatment and the study of this patient possible. Mr. R. H. Noell, Bristol Laboratories, Inc., Syracuse, N. Y., furnished the information on the crystalline penicillin G potassium used.

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THE LIFE HISTORY OF ONE HUNDRED PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE

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ALTHOUGH many attempts have been made to characterize fully the natural history of hypertensive vascular disease, varying diagnostic criteria and problems of selection have imposed obstacles which are difficult to overcome. The problems, requirements, and benefits to be derived from long-term studies have recently been discussed by Evelyn.[1] It is rare, as he pointed out, for data to include an accurate account of the disorder from its incipiency.

TABLE I. STATISTICAL DATA CONCERNING 100 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE FOLLOWED FROM ONSET UNTIL DEATH

	NUMBER AND PER CENT
Men	38
Women	62
Family history of hypertensive vascular disease	26
Onset in association with pregnancy	4
Average age at onset: 32 years (S.D. ±5.9) (range 15–46)	
Average age at death: 51 years (S.D. ±9.2) (range 27–77)	
Average duration of hypertensive vascular disease: 19 years (range 3–34)	
Primary cause of death:	
Not known	41
Congestive failure (not associated with myocardial infarction)	19
Cerebral vascular accident	17
Myocardial infarction	7
Uremia	6
Arteriosclerotic aneurysm of aorta	3
Miscellaneous unrelated causes	7

For this reason and as a preliminary approach to more complete understanding, statistical information has been gathered concerning the life history of 100 patients followed from the time of onset of hypertension until death. This survey has been limited therefore to those patients in whom the first appearance of an abnormal elevation of blood pressure (repeated casual diastolic readings of 90 mm. Hg or more) was a matter of record after a known period of normotension recorded not longer than two years before. Additional requirements included

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the documentation of hypertensive vascular disease, the elimination of subjects whose hypertension was transient, and observation without specific therapy other than the usual conventional methods until death. Normotensive criteria included multiple normal blood pressure determinations in individuals not on bed rest and not obtained during or immediately after acute or febrile illnesses. The label of hypertension was applied, even in those who later exhibited occasional diastolic values of less than 90 mm. Hg, providing that at least three abnormal readings had been obtained and the subsequent course indicated the development of definite disease.

The major statistical facts are presented in Table I.

Additional data, with reference to certain symptoms and complications and with emphasis on their relationship to prognosis, are summarized in Table II.

TABLE II. ONE HUNDRED PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE: SIGNS, SYMPTOMS, AND COMPLICATIONS

	NUMBER AND PER CENT	AVERAGE YEARS BEFORE DEATH
Blood pressures		
Labile (diastolic fluctuations >15 mm. during most of course)	68	
Fixed (diastolic fluctuations <15 mm. during most of course)	32	
Progressive increases once hypertensive vascular disease well established	21	
Average years before death after first recording of systolic >200, excluding terminal cases: 9 (range 1–27)		
Average years before death after first recording of diastolic >120, excluding terminal cases: 9 (range 1–21)		
Average duration of hypertensive vascular disease in those with diastolic values generally >120:14; <120:21		
Retinitis		
Inadequate data	10	
No or mild arteriosclerotic vessels	32	
Moderate or marked arteriosclerotic vessels	26	
Hemorrhages and/or exudates	20	5
Papilledema	12	1
Cardiac hypertrophy (increased silhouette by roentgenogram)		
Inadequate data	30	
No hypertrophy	6	
Hypertrophy	64	7
Electrocardiogram		
Inadequate data	36	
Left axis deviation	34	
Myocardial damage	30	7
Congestive failure	42	5
Angina pectoris	16	7
Myocardial infarction	13	5*
Cerebral vascular accidents	29	3*
Albuminuria (excluding terminal cases)	36	5
Nitrogen retention	24	1

*Excluding cases in which the event caused immediate death.

Several features of this preliminary survey deserve comment. With more precise knowledge as to the time of onset of hypertension, it is again apparent that hypertensive vascular disease begins as a rule in early adult life and has an average duration (close to two decades) which is longer than generally appreciated. Although twenty-four of the women had pregnancies during the period of observation, it is conspicuous that in only four was there any evident relationship between pregnancy and the onset of disease. As hypertension may have preceded conception in two patients in whom the last normotensive readings had been many months before, these data would suggest that sustained elevations of blood pressure after a pregnancy are indicative generally of antecedent disease.

It would be desirable to group these cases according to a classification such as suggested by Palmer and associates.[2] At least such a scheme would serve a real purpose in comparative studies to determine the value of specific therapeutic procedures. It is indeed apparent that multiple complications are more frequent than single, that the time of onset and the intensity of any given complication vary enormously from one situation to another. However, any further breakdown in a preliminary series of this size would result in data of no statistical significance. Nevertheless, measured in terms of single complications, it is noteworthy that an average survival of five or more years may be observed after all complications except in patients who have sustained cerebral vascular accidents or who have exhibited papilledema or nitrogen retention.

SUMMARY

Data are presented concerning the life history of 100 patients with hypertensive vascular disease followed from the onset of hypertension until death. The average duration of the disorder in this group was 19 years, its onset occurring at an average age of 32 years. It is doubtful that pregnancy plays a significant part in initiating the permanent hypertensive state. Additional data are given which emphasize the effect on life span and frequency of certain signs, symptoms, and complications.

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EISENMENGER'S COMPLEX: REPORT OF TWO CASES AND REVIEW OF CASES WITH AUTOPSY STUDY

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THE present interest in patients with congenital heart disease and the extensive surgical therapy now employed in these patients warrant more complete study and analysis of the various types of abnormalities encountered. Well known among the rarer abnormalities is the Eisenmenger complex. The Eisenmenger complex consists basically of two defects within the heart—a high interventricular septal defect and dextroposition of the aortic valve which overrides the septal defect. In addition to the septal defect and the overriding dextroposed aortic valve, enlargement of the right ventricle and enlargement of the pulmonary artery are usually present. There is no pulmonary valvular or infundibular stenosis; this distinguishes this group from the tetralogy of Fallot group. In the latter the pulmonary artery is usually small.

There have been sixteen cases of Eisenmenger's complex reported with pathological study of the heart. These case reports and their sources are presented in Table I. This paper describes two more cases with autopsy findings.

The first case was described by Dalrymple in 1847 in a 25-year-old, cyanotic woman.[4] Fifty years later, Eisenmenger wrote his lengthy report on a 32-year-old man dying of congestive failure.[1] This patient had been followed for many months of his life in von Schroetter's Clinic where a correct diagnosis of congenital heart disease with an interventricular septal defect was made ante mortem. It was Abbott, perhaps the greatest student of congenital heart disease, who christened this group of defects with Eisenmenger's name. She considered this complex as consisting of a ventricular septal defect and dextroposition of the aorta without any pulmonary stenosis or hypoplasia. Abbott, by 1927, had gathered from the literature and her own experience a total of eight cases.[4] Since then, eight more cases have been reported by other investigators.

In addition to the eighteen cases forming the basis for this clinicopathologic study, there have recently been several patients reported who have been diagnosed clinically as having Eisenmenger's complex.[12,11,15] Bing, Vandam, and Gray report interesting physiological studies done by cardiac catheterization in five of these patients.[11]

The embryological basis for Eisenmenger's complex has been described by Abbott[4] and others. Not sufficiently emphasized in previous reports is the frequent association of other cardiac abnormalities with this syndrome. Many workers have shown the frequent association of enlargement of the pulmonary artery and its branches and enlargement of the right ventricle with the two basic

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defects of this complex. In fact, many pathologists include these with the essential criteria for its diagnosis at autopsy and think in terms of the "tetralogy" of Eisenmenger. Even though only eighteen cases have been reported, the following associated abnormalities have occasionally been found: patent ductus arteriosus,[4,10] patent interatrial septal defect,[4,6] hypoplasia of the aorta,[4,7] right-sided aorta,[6] anomalous coronary artery distribution,[3,10] anomalous origin of vessels from the aortic arch,[6] patent foramen ovale,[6] aneurysm of cusps of aortic valve,[2] retraction and insufficiency of the right aortic cusp,[9] and coarctation of the aorta.[10]

The first case reported below had, in association, a patent ductus arteriosus. He was operated upon for the ductus, the presence of an Eisenmenger heart not having been suspected. The second patient had, in association, a moderate coarctation of the aorta.

As the pulmonary valve and pulmonary artery are normal in size or actually enlarged in this complex, surgical operations creating a systemic pulmonary arterial shunt will not be helpful to such patients.

CASE REPORTS

CASE 1.—

History.—The patient was a 3½-year-old boy. He had had persistent intermittent vomiting and a chronic cough during the first nine months of life. Afterward, these symptoms had gradually subsided. He had developed poorly, taking a diet of liquid and semiliquid food. During the first year of life he had had two episodes of pneumonia. He had chronic weakness (shortness of breath on exertion) and was easily fatigued.

Physical Findings.—The blood pressure was 115/70 mm. Hg. There was mild cyanosis of the nail beds. The heart was enlarged, the apex being to the left of the mid-clavicular line on the left. There was questionable enlargement to the right. A systolic thrill was palpable along the left sternal border. In the fourth left intercostal space a "machinery" murmur could be heard, and it was well transmitted in all directions. There was a separate, distinct, harsh, apical, systolic murmur. The liver was palpable 2 to 3 cm. below the right costal margin. The spleen was barely palpable. Phimosis of the penis was present.

Roentgenogram.—X-ray examination revealed cardiac enlargement, markedly enlarged pulmonic vessels, left-sided aorta, pulmonary congestion, and no pressure deviation of the esophagus.

Electrocardiogram.—The electrocardiogram showed left axis deviation, inversion of T waves in CF_3 and CF_4, and diphasic T waves in CF_1 and CF_2.

Laboratory Findings.—The hemoglobin was 15.0 to 12.2 Gm. per 100 c.c. of blood, the red blood cell count 4.3 million per cubic millimeter of blood, and the hematocrit 38 volumes per cent. The leucocyte count was 11,100 per cubic millimeter of blood, the Kahn and Wassermann reactions negative, blood cultures sterile, and urine negative.

Hospital Course.—It was decided that the patient had a patent ductus arteriosus, as well as other congenital lesions of the heart, and an operation for ligation of the ductus was undertaken. The operation disclosed an extremely large vessel in the position of the pulmonary artery, and ligation of the ductus was abandoned. As the chest was closed, the child suddenly died, and efforts for resuscitation were unsuccessful.

Clinical Impressions.—The clinical impressions were: congenital heart disease with patent ductus arteriosus;? persistent aortic ring;? septal defect; phimosis.

Autopsy Findings.—

General: The body was that of a poorly developed, white boy, 92 centimeters long, weighing approximately 25 pounds. The lips and nail beds were cyanotic. There was slight bulging of the left anterior chest wall. The penis was uncircumcised and presented marked phimosis. About

TABLE I.

NO.	CASE REPORTED BY	AGE (YEARS)	SEX	CYANOSIS	DYSPNEA	CLUBBING	MURMURS		CHEST DEFORMITY	UNDER-DEVELOP-MENT
							SYSTOLIC	DIASTOLIC		
1	Dalrymple	25	F	Yes						
2	Eisenmenger[1]	32	M	Yes	Yes	Yes (mild)	Yes	Yes (terminal)	Precordial bulging	No
3	Abbott (Libman)[2]	33	M	No	Yes	Yes	Yes	No	No	No
4	Abbott[2]	22	M	Yes	Yes					
5	Baumgartner[3] and Abbott	20	M	Yes	Yes (after exertion)	No	Yes	Yes	No	No
6 7 8	Abbott[4] (8 cases including the 5 listed above)	4 mo. to 33 yr.		Slight, 2; moderate, 1; marked, 4; absent, 1	3 cases	2 cases	4 cases	2 cases	2 cases	2 cases
9	Stewart and Crawford[5]	60	M	Yes (4 months)	Yes (1 year)	No	Yes	No	No	No
10	Rosedale[6]	10	M	Yes (on exertion)	Yes (on exertion)	Yes (moderate)	Yes	No	Right chest wall bulge	No
11	Talley and Fowler[7]	31	F	Yes (always)	Yes (on exertion)	Yes (marked)	Yes	Yes (pulmonic slight)		
12	Miller and Kornblum[8]	32	F	Yes	No	Yes (slight)	Yes	Yes	No	No
13	Taussig and Semans[9]	7	M	No	No	No	Yes	Yes (aortic)	No	No
14	Saphir and Lev[10]	21	M	Yes	Yes (on exertion)	Yes (marked)	Yes	Thrill (pulmonic)	Lower sternum bulge	Yes
15	Eppinger, Burwell, and Farher[11]	27	F	Yes (after 16)		Yes	Yes	Yes (pulmonic)	No	No
16	Hurst and Schemm[14]	21	F	Yes (transient)	Yes	No	Yes	Yes (machinery)	No	Mental not physical
17	Case 1	3	M	Yes (on exertion)	Yes (on exertion)	No	Yes	Yes (machinery fourth left intercostal space)	Slight bulge left chest wall	Yes
18	Case 2	22	F	Yes	Yes (on exertion)	Yes (moderate)	Yes	No	No	Yes (physical

I.

OTHER	BLOOD COUNTS	I. V. SEPTAL DEFECT	DEXTRO-POSITION	CARDIAC HYPERTROPHY		ENLARGEMENT OF PULMONARY ARTERIES	PATENT DUCTUS ARTERIOSUS	PATENT AURICULAR SEPTUM	HYPO-PLASIA OF AORTA	RIGHT-SIDED AORTA
				RIGHT	LEFT					
		Yes	Yes							
		Yes	Yes	Yes	No	Yes	Obliterated	No		
		Yes	Yes	Yes	Yes 2.0 cm.	No				
		Yes	Yes	Yes 1.5 cm.	Yes 1.3 cm.	Yes				
Fatigue, hoarseness, aphonia		Yes	Yes	Yes 1.0 cm.	Yes 1.2 cm.	Yes				
		8 cases	8 cases	8 cases	6 cases	4 cases	1 case patent	2 cases	2 cases	
Fatigue, 1 year; weakness, 1 year		Yes	Yes	Yes 2.0 cm.	Yes 2.0 cm.	Yes	Obliterated			
	Hgb. 80%; RBC 5.1 M.	Yes	Yes	Yes 1.5 cm.	Yes 1.8 cm.	Yes	Obliterated (2×0.4 cm.)	Yes		Yes
	Highest Hgb. 120%; 88% average	Yes	Yes	Yes 1.5 cm.	Yes 3.0 cm.	Yes			Yes	
Epistaxis, vertigo, hoarseness	Hgb. 70–57%; RBC 5.3 M.	Yes	Yes	Yes 0.8 cm.	No 1.2 cm.	No				
	RBC 3.85 M.	Yes	Yes	Yes 0.5 cm.	Yes 1.3 cm.	No	Obliterated			
		Yes	Yes	Yes 1.2 cm.	Yes 1.1 cm.	Yes	Widely patent			
	RBC 8.0 M.; Hgb. 19.0 Gm.	Yes	Yes	Yes (?)	Yes (?)	Yes				
Epistaxis, palpitation		Yes	Yes	Yes 1.0 cm.	Yes 2.0 cm.	Yes (moderate)	Obliterated			
Weakness, fatigue	RBC 4.3 M.; Hgb. {15.0 Gm. 12.2	Yes	Yes	Yes 0.7 cm.	Yes 1.4 cm.	Yes	Patent			
Weakness, fainting, epistaxis	RBC 4.2 M.; Hgb. 12.5 Gm;	Yes	Yes	Yes 1.3 cm.	Yes 1.4 cm.	No	Obliterated (2×0.5 cm.)			

100 c.c. of serous fluid were present in the peritoneal cavity, 200 c.c. of sanguinous fluid in the left pleural cavity, and 40 c.c. of serosanguinous fluid in the right pleural cavity. Slight congestion was present in both lungs. The liver weighed 550 grams (normal about 450 grams). The spleen weighed 73 grams (normal about 38 grams). The brain showed no abnormalities.

Heart: The heart was markedly enlarged and measured 9 by 7 by 6 cm. (Figs. 1 and 2). The pulmonary artery was very large, its circumference being 5.4 cm. (as compared with the aorta which appeared normal in size, with a circumference of 2.5 cm.). This pulmonary arterial dilatation extended into the smaller radicles of the arterial tree of the lungs. The ductus arteriosus measured 1.1 cm. in length and 5 mm. in diameter. It was patent with a lumen measuring 2 mm.

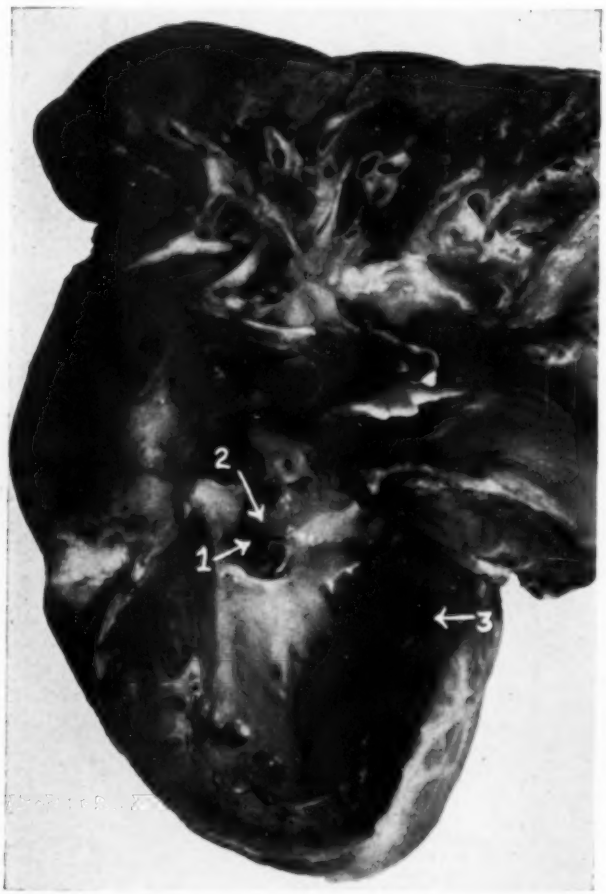

Fig. 1.—View into left ventricle (Case 1), showing: *1*, high interventricular septal defect, *2*, overlying dextroposed aortic valve, and *3*, left ventricular hypertrophy.

in diameter. The aorta descended normally on the left side of the vertebral column. The ventricular walls were hypertrophied, the right ventricle measuring 7 mm. in thickness and the left ventricle 14 mm. in thickness. The right atrium was dilated. There was a high interventricular septal defect, measuring 5 by 8 mm. In this defect there was a network (of Chiari) consisting of four to five interlacing fibrous strands. Overriding this defect, chiefly on the left ventricular side, was the aortic valve. The coronary ostia were patent, opening rather high above the sinuses of Valsalva. There was no interatrial septal defect, and the foramen ovale was closed. The heart valves showed no abnormalities; they measured (in circumference) as follows: tricuspid, 6.5 cm.; pulmonic, 5.0 cm.; mitral, 7.0 cm.; and aortic, 4.5 cm. There was no subpulmonic stenosis.

Microscopic Examination.—The lungs showed marked capillary congestion and occasional mononuclear cells within the alveoli. The pulmonary arteries showed medial hypertrophy. Otherwise, no significant changes were seen.

Anatomical Diagnoses.—The diagnoses were: (1) Eisenmenger's complex, with enlargement of the pulmonary artery and its radicles, (2) cardiac hypertrophy, (3) patent ductus arteriosus, (4) generalized muscular and skeletal underdevelopment, (5) left hemothorax (surgical), (6) phimosis.

CASE 2.—

History.—The patient was a 22-year-old, white housewife. She was admitted to the North Carolina Baptist Hospital for study because of the association of pregnancy and cyanotic congenital heart disease. She stated that she had had heart trouble all of her life. She had noted cyanosis of the lips and finger tips following exertion for as long as she could remember, but stated that this cyanosis was not evident immediately from birth. She also had had dyspnea on exertion

Fig. 2.—View of great vessels (Case 1), showing: *1*, aorta, *2*, ductus arteriosus, *3*, markedly enlarged pulmonary artery, and *4*, enlarged radicle of pulmonary artery.

and was unable to run and play as other children. On slight exercise she was prone to get spots in front of her eyes and she would "black out." She had never experienced precordial pain, ankle edema, or orthopnea. During her childhood she had three attacks of pneumonia. Her appetite had always been poor, and her weight had ranged from 80 to 89 pounds since she was grown. At the age of 11 years she had had a severe epistaxis but had noted none in recent years. She had hematuria following a tooth extraction three years prior to admission and a period of jaundice two years before admission.

Physical Findings.—The patient was examined in the outpatient department of this hospital four years prior to her first hospital admission. At that time the blood pressure was 106/78 mm. Hg, and there was heard a moderately loud, harsh, systolic murmur over the precordium, loudest in the fourth left intercostal space about 4 cm. from the mid-sternal line. There was also a systolic thrill palpable in the same area. The second pulmonic sound was accentuated. The heart was not enlarged. The lungs were clear.

Examination of the patient at the time of the first admission (May 18, 1950) revealed a rather small, somewhat undernourished, pregnant (seven months) woman. There was cyanosis evident in the lips and finger tips. There was slight clubbing of the fingers. The blood pressure was 152/94 mm. Hg. The heart was not enlarged. The sounds were forceful; the second sound in the pulmonic area was very loud and was palpable, along with a systolic thrill in the same area. There was a rather short, moderately loud, systolic murmur along the left sternal border in the second and third intercostal spaces. This murmur was loudest about 6 cm. from the mid-sternal line in the third intercostal space. The second pulmonic sound was markedly accentuated. There was no enlargement of the liver and no ankle or sacral edema. The lungs were clear.

On the last hospital admission (June 2, 1950) the physical findings were essentially the same as before. The apex of the heart was located 10 cm. from the mid-sternal line. There was some distention of the neck veins.

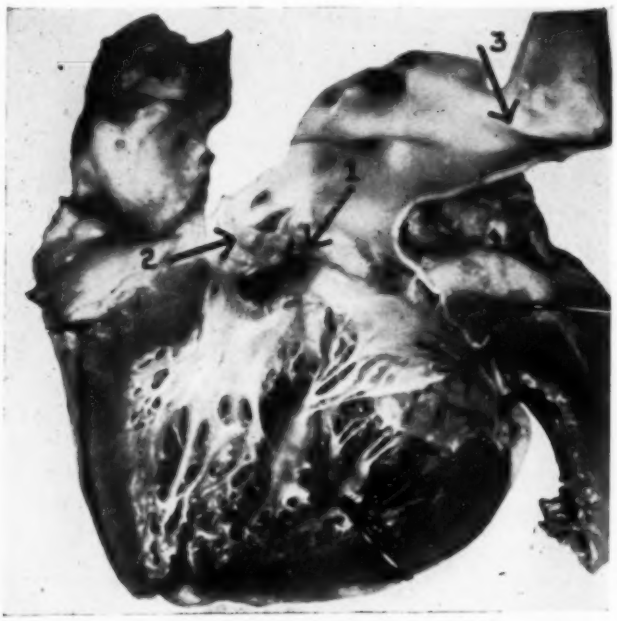

Fig. 3.—View into left ventricle (Case 2), showing: *1*, high interventricular septal defect, *2*. overlying dextroposed aortic valve, and *3*, coarctation of the aorta.

Roentgenogram and Fluoroscopy.—The heart was slightly enlarged. There was bulging of the contour in the region of the pulmonary conus and prominent pulmonary arteries. The lungs were clear.

Electrocardiogram.—The electrocardiogram showed abnormal right axis deviation (128 degrees), small P waves throughout, deep S waves in Leads I, V_2, V_4, V_5, and aV_L, and intrinsic deflections of 0.04 second in V_1, 0.05 second in CF_1, and 0.02 second in V_6. The interpretation was: right ventricular hypertrophy with no atrial enlargement.

Laboratory Findings.—The hemoglobin was 15.0, 13.0, and 13.5 Gm. per 100 c.c. of blood, the red blood cell count 4.1 and 4.0 million per cubic millimeter of blood, the white blood count 7,200 with a normal differential count, and the Kahn test negative. Urinalysis showed a trace of albumin and an occasional white blood cell per high-power field. The blood urea nitrogen was 13.5 mg. per 100 c.c.

Hospital Course.—The first hospital admission was uneventful. On the fourth hospital day of the second admission, while using the bedpan, the patient developed marked dyspnea and weakness. With this, the cyanosis became more intense. Digitalis was begun, and oxygen was

administered by nasal catheter. The following day she suddenly developed pulmonary edema, with moist, bubbling râles in both lungs. The heart rate was 180. Cyanosis was quite intense again. She was given intravenous aminophylline, and the condition rapidly improved. Quinidine was begun by mouth. On the following day, while the linens were being changed, she again developed sudden dyspnea, cyanosis, and weakness. Bright vaginal bleeding in small amounts was noted. The uterus was contracted and firm. Later she became disorientated after a sudden episode of dyspnea and cyanosis. Râles were present at both lung bases. She was given positive pressure oxygen, aminophylline intravenously, Coramine, and intracardiac Adrenalin. She showed no response to these measures and died.

Clinical Impressions.—The clinical impressions were: congenital heart disease —? Eisenmenger's complex, ? single ventricle with interatrial septal defect; intrauterine pregnancy with premature rupture of the membranes; pre-eclamptic toxemia.

Autopsy Findings.—

General: The body was that of a rather thin woman of small stature. There was slight clubbing of the fingers. No chest deformity was noted. The uterus was enlarged, and it contained a male fetus weighing 1,500 grams. The placenta was completely separated from the uterine wall, and the uterine cavity contained about 300 c.c. of partially clotted blood. The brain and other organs showed no significant gross lesions.

Heart and pericardium: The pericardial cavity contained about 100 c.c. of yellow serous fluid. The pericardium itself was smooth and glistening throughout. The heart weighed 300 grams and externally did not appear enlarged (Fig. 3). The atria were rather small in size, and the musculature appeared normal in thickness. The left ventricle showed slight hypertrophy, and it measured 1.4 cm. in thickness. The right ventricle was markedly hypertrophied, and it measured from 0.8 to 1.3 cm. in thickness, the hypertrophy being most evident in the region of the pulmonary conus. There was no interatrial septal defect. There was a high interventricular septal defect in the membranous portion of the septum. This defect measured 13 by 12 mm. Overriding this defect was the aortic valve, which showed about 25 per cent of the valvular opening lying over the right ventricular cavity. There was no infundibular (subpulmonic) stenosis. The heart valves themselves showed no abnormalities. Their circumferences were as follows: mitral, 8.0 cm.; pulmonic, 6.0 cm.; tricuspid, 9.5 cm.; and aortic, 6.0 cm. The pulmonary artery measured 48 mm. in circumference 3 cm. above the pulmonic valve. The aorta measured 47 mm. in circumference about 3 cm. above the aortic valve; the vessel size remained approximately the same until one reached the point of the aorta at which the ligamentum arteriosum is attached, where the circumference rather abruptly decreased to 27 mm. The aorta distal to this point measured 31 mm. in circumference. The ductus arteriosus was closed; it measured 20 mm. in length and 5 mm. in diameter.

Anatomical Diagnoses.—The diagnoses were: (1) Eisenmenger's complex, (2) moderate coarctation of the aorta, (3) pregnancy, with a 1,500 gram fetus in utero, (4) complete placental separation.

CLINICAL FEATURES

The development of cyanosis at some time of life is a fairly characteristic feature, but it is usually minimal except in the presence of failure or complicating pulmonary disease. In most cases it is very evident preceding death. There have been two cases reported that never showed cyanosis: one an infant of 15 months reported by Abbott,[4] and the other a 7-year-old boy who died of bacterial endocarditis and aortic insufficiency, reported by Taussig and Semans.[9] Stewart and Crawford's patient lived until 60 years of age with cyanosis occurring only during the last few months of life.[5] Most of the patients, however, had cyanosis evident constantly, or on exertion and straining, for many years of their lives.

Dyspnea on effort occurred in the patients with significant cyanosis, and these two symptoms usually were noted simultaneously.

TABLE II. SIGNS AND SYMPTOMS REPORTED IN PATIENTS WITH EISENMENGER'S SYNDROME (18 CASES)

	NO. PATIENTS
1. Cyanosis	16
2. Systolic murmur	14
3. Dyspnea	11
4. Clubbing	8
5. Diastolic murmur	8
6. Chest deformity	5
7. Underdevelopment	5
8. Weakness and fatigue	4
9. Epistaxis	3
10. Hoarseness	1

One should expect a systolic murmur to be present in every case. It was heard and described in fourteen of the patients. Its characteristics are those of all murmurs of interventricular septal defects—harsh, loud, along the left sternal border in the second to fourth intercostal spaces. The murmur in our second patient was not characteristic at the time of the final admission, but it had been typical four years before. In the last trimester of pregnancy the heart is displaced, and this might account for the systolic murmur being heard above and to the left of the usual location. A diastolic murmur was surprisingly frequent, due perhaps to several causes, insufficiency of pulmonic valve, patent ductus arteriosus, or aortic insufficiency. The characteristics of the diastolic murmur varied with the cause. It has been stated that the systolic murmur of an Eisenmenger heart does not radiate into the neck vessels, as does the murmur of tetralogy of Fallot (since the pulmonic valve is stenosed in the latter, little blood leaves the heart by this orifice, and murmurs are transmitted with the flow of blood).[1] Others have reported that this sign is not always present.

Clubbing of the terminal phalanges was present in eight of the cases. It is not as striking or as constant as in the tetralogy of Fallot.

TABLE III. PATHOLOGICAL FINDINGS OTHER THAN SEPTAL DEFECT AND DEXTROPOSITION OF AORTIC VALVE (18 CASES)

	NO. PATIENTS
1. Hypertrophy of right ventricle	18
2. Hypertrophy of left ventricle	14
3. Enlargement of pulmonary artery	11
4. Patent ductus arteriosus	3
5. Patent auricular septal defect	3
6. Hypoplasia of aorta	3
7. Aneurysm of cusp of aortic valve	2
8. Atypical coronary artery distribution	2
9. Coarctation of aorta	2
10. Dextroposition of aorta	1
11. Anomalous distribution of vessels from arch	1
12. Retraction and insufficiency of aortic cusps	1

TABLE IV. DIFFERENTIAL DIAGNOSTIC FEATURES IN PATIENTS WITH EVIDENT VENTRICULAR SEPTAL DEFECT LIVING BEYOND SIX MONTHS OF AGE

	CYANOSIS, DYSPNEA, CLUBBING	POLYCYTHEMIA	X-RAY AND FLUOROSCOPY OF HEART AND GREAT VESSELS	ELECTROCARDIOGRAM	LENGTH OF LIFE
Eisenmenger's complex	Usually present, usually slight	Often absent	Enlargement of heart (generalized), right heart and pulmonary conus prominent	Usually normal axis or left axis deviation, occasionally right axis deviation	4 mo.-60 yr. (generally 10-35 yr.)
Tetralogy of Fallot	Usually severe	Usually present	Normal size or right ventricular enlargement, pulmonary conus absent, absence of hilar shadows	Usually marked right axis deviation	Few months-60 yr. (generally 2-15 yr.)
Septal defect only	Rare	Absent	Usually normal size, occasionally prominent pulmonary conus	Usually normal axis deviation	Normal (unless subacute bacterial endocarditis develops)
Truncus arteriosus	Usually absent	Usually slight	Prominent aortic knob, greatly enlarged (especially left ventricle), indentation of or absence of pulmonary conus	Usually normal axis deviation	Usually die before maturity
Atrioventricularis communis	Never conspicuous	Absent	Slight enlargement of right ventricle	Occasionally partial heart block (2:1)	Usually early adult life (frequently in Mongolian idiots)

Of the other symptoms only chest deformity, underdevelopment, weakness, and fatigue would seem to be important. Probably weakness and easy fatigue are more prominent than reported.

Cardiac hypertrophy is a constant feature and should be evident on x-ray examination and fluoroscopy. An enlarged pulmonary conus was seen in five of eight roentgenograms taken. One electrocardiogram showed left bundle branch block in a 20-year-old man; all electrocardiograms (seven reported) have shown abnormal left axis or normal deviation except Case 12 and the second case reported here. This may aid in differential diagnosis, especially in distinguishing this syndrome from the tetralogy of Fallot (see Table IV). Polycythemia is relatively uncommon, being reported in only two cases. However, blood counts were given in only seven cases.

In any patient with signs of cardiac hypertrophy, interventricular septal defect, and chronic mild hypoxia (cyanosis, dyspnea, clubbing), the diagnosis of Eisenmenger's complex should be entertained. In cases of patients with prominence of the pulmonary conus by roentgenogram, abnormal left axis or normal axis deviation on the electrocardiogram, absence of polycythemia, and life beyond adolescence, one may make the diagnosis. Other defects (as patent ductus, hypoplasia of the aorta, and so forth) are prone to occur and should not alter the diagnosis.

TABLE V. CAUSES OF DEATH IN EISENMENGER'S COMPLEX

	NO. CASES
Heart failure	7
Bacterial endocarditis	4
Bronchopneumonia	1
Cerebral abscess	1
Unknown	5

SUMMARY

Two cases of Eisenmenger's complex are described. The total number of such cases reported with pathological study is eighteen. The clinical and pathological findings in these patients are tabulated and discussed. Suggested diagnostic criteria, on the basis of these proved cases, are given.

The first case is the third reported having associated with it a patent ductus arteriosus. The second case is the second reported having coarctation of the aorta associated with Eisenmenger's complex. Such associated anomalies are frequent.

Appreciation is expressed to Thomas N. Lide, M.D., and Robert L. McMillan, M.D., for their advice and assistance.

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CONGENITAL HEART DISEASE IN PREGNANCY

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WHEN pregnancy occurs in a woman who has heart disease, the latter is most commonly rheumatic in origin. The relative infrequency of congenital heart disease accounts for the slight consideration given it in most discussions of heart disease in pregnancy, and it seems propitious to call attention to the problem at this time. It is the purpose of the present report to record a series of thirty-three patients, representing eighty deliveries, seen in the past ten years in the Charity Hospital at New Orleans, in order to add to the meager data existing in the literature.

MATERIAL AND METHODS

Records from Charity Hospital at New Orleans for the past ten years were reviewed. All patients had been seen by consultants from the cardiac service and, in a number of instances, by the authors personally. The diagnoses were based primarily on the clinical picture with special emphasis on a careful fluoroscopic examination. In five instances cardiac catheterization supplemented the usual diagnostic measures. In all instances it was decided that congenital heart disease was present, and in all but four the anatomical diagnosis seemed reasonably certain. There were twenty Negro patients in the group and thirteen white patients. The diagnoses are given in Table I.

Data.—In forty-three of the eighty pregnancies (Table II)[14] the patients were classified in Group I A throughout pregnancy. Of those starting pregnancy in I A, two patients deteriorated to I B, one to III C, and two to IV E. The patient who progressed to III C had the picture of post-partum heart disease. One of the patients who deteriorated to IV E had failure precipitated by anemia and high post-partum fever; the other went into sudden fatal post-partum vascular collapse.

Of twenty-six patients who were in Class I B at the beginning of pregnancy, only one, a patient having coarctation of the aorta, changed status to III C, and this occurred in labor. Two patients were in Class III C throughout, and a third changed from III C to IV E during the last trimester.

Between pregnancies one patient changed from I A to I B, one from I A to II B, and one from I B to III C.

In the eight patients with interatrial septal defect, sixteen pregnancies occurred. On thirteen occasions the patient remained in Class I A throughout

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pregnancy. One patient in Class I B did not change status; one patient changed from I A to I B during pregnancy and then to IV E in the post-partum period. One patient in Class III C progressed to Class IV E. No change from one class to another occurred within this group in subsequent pregnancies.

TABLE I.

DIAGNOSIS	NO. PATIENTS	NO. PREGNANCIES
Interatrial septal defect	8	16
Interventricular septal defect	6	14
Patent ductus arteriosus	5	18
Coarctation of aorta	5	11
Pulmonary stenosis	3	12
Tetralogy of Fallot	2	3
Undiagnosed congenital heart disease	4	6
Total	33	80

TABLE II.

DIAGNOSIS	CLASS	BEFORE OR EARLY IN PREGNANCY	LATER IN PREGNANCY OR PUERPERIUM
Interatrial septal defect	I A	14	13
	I B	1	2
	III C	1	0
	IV E	0	2
Interventricular septal defect	I A	10	9
	I B	3	3
	III C	1	1
	IV E	0	1
Patent ductus arteriosus	I A	6	5
	I B	5	6
	II B	6	6
	III C	1	1
Coarctation of aorta	I A	1	1
	I B	10	9
	III C	0	1
Pulmonary stenosis	I A	11	10
	I B	1	2
Tetralogy of Fallot	I B	3	2
	IV E	0	1
Unclassified	I A	3	3
	I B	3	3

The six patients with interventricular septal defect had fourteen pregnancies. In nine, the patients remained in Class I A throughout pregnancy. One changed from I A to IV C due to the development of post-partum heart disease. One patient in Class I B went through three pregnancies without change. One pa-

tient in Class III C remained stationary despite anemia and sarcoma. She changed from I B to III C between pregnancies.

Eighteen pregnancies occurred in the five patients with patent ductus arteriosus. In five pregnancies the patients remained in Class I A, in five in Class I B, in six in Class II B, and in one in Class III C throughout. One patient changed from Class I A to I B. With the fourth pregnancy, one patient became II B, but reverted to I A in the fifth pregnancy.

Five patients with coarctation of the aorta had eleven pregnancies. One patient remained in Class I A throughout pregnancy, and in nine other pregnancies the patients remained in Class I B. One changed to Class III C. None changed status between pregnancies. In one patient the blood pressure in pregnancy was lower than the prepregnant level, and the eye grounds changed from grade III to grade I. Only one instance of toxemia occurred in the group. No instances of cerebral vascular accidents or rupture of the aorta were noted.

There were twelve pregnancies in the three patients with pulmonic stenosis. In ten pregnancies the patients remained in Class I A and in one in Class I B. In only one patient did the status change, and this was from I A to I B in the sixth pregnancy at the age of 37 years.

Three pregnancies occurred in two patients with the tetralogy of Fallot. One patient was in Class I B in two pregnancies despite the occurrence of subacute bacterial endocarditis in the second. The other patient, after failing in pregnancy, died in vascular collapse at delivery.

We have included as undiagnosed congenital heart disease four patients in whom a diagnosis as to anatomical defect was not certain. There were six pregnancies in these patients; in three the patients were classed as I A and in three as I B. No change in the status occurred. In none of these were the newer diagnostic methods of catheterization and contrast visualization utilized. Such methods, if employed, might have enabled us to make a more exact diagnosis.

Of the eighty full-term pregnancies, heart failure occurred in seven. Of these, one fitted the pattern of post-partum heart disease; another developed congestive heart failure in the post-partum period in the presence of high fever and anemia; and a third had a severe anemia due to sarcoma. In the remaining four heart failure was uncomplicated. Only one death, in a patient with the tetralogy of Fallot, occurred in the series.

Pertinent facts in the histories of those patients developing congestive heart failure are as follows:

CASE 1.—An 18-year-old Negro woman, who was known to have been cyanotic since birth and who had noted slight dyspnea all her life, developed toxemia at the twenty-fourth week of the first pregnancy. Examination revealed findings typical of tetralogy of Fallot, and this diagnosis was confirmed by cardiac catheterization. The blood pressure was 156/118 mm. Hg. The urine contained 4 plus albumin. Pulmonary edema, pedal edema, and high venous pressure were evident. Digitalization was started. Precipitously, in the twenty-sixth week, she delivered a stillborn infant, went into vascular collapse, and died within an hour. At post-mortem examination the tetralogy of Fallot with infundibular stenosis and a bicuspid pulmonary valve was demonstrated.

CASE 2.—A 20-year-old Negro woman with murmurs typical of patent ductus arteriosus since the age of 5 years had been dyspneic and orthopneic for eight years before the first pregnancy. At

times râles were present in the lung bases. She was carried through pregnancy on digitalis. Delivery was uneventful with low forceps. She improved after delivery, but was never out of mild failure. Two months after delivery, during an operation for the patent ductus, she died as a result of an inadvertent tear of the ductus.

CASE 3.—A white woman with interatrial septal defect, confirmed by catheter studies, had an uneventful pregnancy at the age of 20 years. At the age of 33 years in the first trimester of the second pregnancy she went into failure. Digitalis was used, but failure progressed. The last six weeks were spent in bed, and delivery by low forceps was accomplished without difficulty. Improvement occurred for four months after delivery, when failure again ensued; it has persisted in mild form for the subsequent two years.

CASE 4.—A 30-year-old white primipara, with the findings typical of coarctation of the aorta, was known to have had a large heart and a systolic blood pressure over 200 mm. Hg since the age of 17 years. She developed congestive heart failure during the labor of the first pregnancy and was digitalized. Three months later, with continued cardiac therapy, she was out of failure.

CASE 5.—A 20-year-old, feeble-minded Negro woman was seen in the fifth month of the first pregnancy. The heart was enlarged. Edema and anemia were present. Physical findings and catheter studies led to the diagnosis of an interatrial septal defect. Six days after the delivery of a 3 pound 8 ounce infant, severe heart failure appeared. The heart increased in size, and high fever was present. With bed rest and antibiotics, compensation was restored. Three months later she was asymptomatic, and the heart size was normal.

CASE 6.—A Negro woman, who had been dyspneic since the age of 12 years, had the physical findings of interventricular septal defect. A normal pregnancy had been accomplished at the age of 22 years. Three years later, a diagnosis of reticulum-cell sarcoma was made and x-ray treatment started. The hemoglobin was then 44.0 per cent, and the heart was enlarged. At the age of 27 years, in the eighth month of the second pregnancy, dyspnea increased, and she was digitalized. A hard labor without untoward reaction was accomplished by low forceps. On the sixth post-partum day she was sterilized.

CASE 7.—A 24-year-old Negro woman was admitted to the hospital in congestive heart failure three weeks after the second pregnancy. The heart was enlarged, and there was a systolic thrill in the third left intercostal space. Bed rest achieved good response. It was felt that this patient probably had post-partum heart disease in addition to the congenital defect.

A history of failure before pregnancy was given by three patients. Of these, one, with patent ductus arteriosus, remained in Class III B throughout pregnancy; a second, with an undiagnosed type of congenital heart disease, had a mild episode of congestive failure four years before pregnancy and remained in Class II B throughout; the third, another patient with patent ductus arteriosus, had had slight dyspnea all her life and was classed as I B during pregnancy. An additional patient with patent ductus arteriosus had developed heart failure in a previous pregnancy, the fourth, but reverted to Class I A in the fifth.

Later in life, subsequent to the pregnancies, four patients exhibited heart failure. One patient with coarctation of the aorta failed at the age of 21 years after six pregnancies; one with patent ductus arteriosus failed at the age of 30 years, two years after the seventh pregnancy. Both of these had a history of toxemia of pregnancy. One patient with interatrial septal defect who had had two normal pregnancies in the early twenties failed at the age of 40 years. At the age of 43 years another patient with interatrial septal defect who had had five normal pregnancies earlier in life showed heart failure. Ten years later, she was still in mild failure.

Twenty-one patients had actual or potential shunts from the arterial to the venous circulation in the heart or great vessels (Table I). Cyanosis was present in only two instances, the patients with tetralogy of Fallot. One of these died in post-partum peripheral collapse; the other developed subacute bacterial endocarditis during pregnancy. She recovered under penicillin therapy and delivered uneventfully. Since it has been available, penicillin has been used prophylactically in the post-partum period in the entire group of congenital cardiac patients.

By physical examination or by x-ray criteria, twenty-five patients were believed to have cardiac enlargement before or early in pregnancy. Later in pregnancy or in the puerperium, the hearts of twenty-nine patients met such criteria.

Only seven of the pregnancies occurred in patients beyond the age of 30 years. One patient with pulmonary stenosis had the third to sixth pregnancies at the ages of 32, 34, 36, and 37 years. Before the last, the status changed from I A to I B. The patient with interatrial septal defect who developed congestive failure did so at the age of 33 years. The others beyond the age of 30 years showed no change from the status in previous pregnancies.

Toxemia of pregnancy occurred ten times in four patients. A patient with patent ductus arteriosus exhibited hypertension in each of the first four pregnancies. The hypertension thereafter became permanent. Two years after the seventh pregnancy, heart failure occurred. A patient with interventricular septal defect had hypertension with each of four pregnancies at the ages of 20, 24, 28, and 30 years. In the fourth pregnancy, at the age of 18 years, a patient with coarctation of the aorta had mild toxemia. Two subsequent pregnancies were normal, but heart failure occurred one year after the last at the age of 21 years. The patient who died of toxemia and heart failure after delivery has been mentioned previously.

Because of dystocia, cesarean section was performed in four instances. All were uneventful. Two of the patients were in Class I A; the third, in whom two sections were performed, was in Class I B on both occasions. The diagnoses were interatrial septal defect, pulmonic stenosis, and interventricular septal defect. In no instance was cesarean section performed for cardiac reasons. Low forceps were used in six deliveries, three being in patients who were in heart failure at the time. All other deliveries were spontaneous.

DISCUSSION

The many problems in the management of heart disease in general during pregnancy are, of course, important when the heart disease is congenital. Recent reviews[1] of the general aspects make it unnecessary to comment on these problems in pregnancy except as they relate to congenital heart disease.

According to the literature, congenital lesions account for 1.5 to 2.5 per cent of the cardiac disease in pregnancy.[2] The forms of congenital heart disease encountered would be expected to be those which permit a woman to reach childbearing age and which, in addition, permit life associations and relationships which lead to marriage. Table I indicates that, in general, this is what happened in our group.

It is the opinion of the authors that the divergent views on the management of congenital heart disease in pregnancy stem from the inadequacy of the number of cases studied. The number of cases now reported is not large enough to give more than rough trends. When it is realized that in his wide experience Mackenzie[4] saw but one instance of pregnancy in a patient with congenital heart disease, it becomes apparent that it will probably not be the good fortune of any one individual to see enough of these patients to form valid conclusions. The recent notation by Hamilton[4] that he has now seen sixty-nine of these cases may prove a legitimate exception. We look forward to a detailed report of these cases. It is felt that reports of series of moderate sizes from various centers will allow a true picture of the problem to emerge. It is with this purpose that we have reported the courses of our thirty-three patients.

Various authors have emphasized different facets of the problem of management. Hamilton and Thomson[5] have cautioned against peripheral collapse attending the rapid emptying of the gravid uterus. Mendelson and Pardee[6] have stressed the importance of charts of pulse and respiration during the course of labor. Lund[7] has noted a relatively high incidence of toxemia in his group and wide swings of blood pressure during labor, often followed by hypotension.

There is considerable variation in mortality rates in the reported series, for they are made up of small groups of patients with heterogeneous lesions of varying severity. All in all, the mortality rate is generally higher than that for heart disease in general (chiefly rheumatic heart disease) in pregnancy, which, with supervision, is approximately 3 per cent.[8] Data in the literature do indicate that the hazard of pregnancy in patients with certain congenital anatomic defects is higher than in those with other types of heart disease. For example, Mendelson and Pardee[6] reported that in thirty-six collected cases of interventricular septal defects, there were four deaths (12.5 per cent). In thirty-one reported instances of patent ductus arteriosus, there were six deaths (19.3 per cent). These findings at least suggest that pregnancy is more dangerous in the presence of congenital heart disease than in the rheumatic type.

Our series is a more optimistic one. There was but one death in the thirty-three, and only four patients developed congestive heart failure as the result of pregnancy. Thus, the mortality and failure rates were 3 and 12 per cent, respectively. In the collected series of Jensen[9] the mortality rate was 20 per cent, and in Hamilton's group[5] it approximated 7 per cent. Not only was the mortality rate low in our series, but it contains many instances of repeated pregnancies without complications. This encouraging result was achieved despite the very low economic status of the group, the resultant poor hygiene, and the absence of a specialized obstetrical cardiac service.

In at least one way pregnancy adds a circulatory defect—the function of the placenta as an arteriovenous aneurysm—which is, in effect, equal to the temporary addition of another congenital anomaly, and this strain, together with the increased load of pregnancy, may be sufficient to precipitate into failure a previously compensated heart with reduced reserve.

In our group of thirty-three patients there were thirteen with communications between either the ventricles or the greater or lesser arterial systems and

eight with interatrial septal defects. Those lesions giving arteriovenous shunts have been reported as adding a hazard unpredictable by the functional classification. Hamilton's warning against rapid emptying of the uterus is based upon his experiences[5] in which sudden release in peripheral pressure, as in cesarean section or version, led to reversal of flow through the shunts. Serious complications and sudden death due to circulatory collapse ensued. In our group of patients with arteriovenous communications, this clinical picture developed but once despite the fact that it was a potential hazard in twenty-one patients. This one instance resulted in death and is the only recorded instance since Hamilton's report of this dreaded vascular collapse in patients with shunts. Our experience suggests that, although such a situation is possible, its likelihood is not apparentlp great. Still, precautions against the development of peripheral collapse in this group are advisable. A forewarning of this possibility was noted by Lund[7] who witnessed wide swings in pulse pressure in these patients. The thirteen cases observed by Lund had stormy courses, one of them dying and nine of them exhibiting congestive failure as pregnancy progressed.

A second anomaly to which pregnancy appears to add a hazard without regard to functional capacity is coarctation of the aorta. In forty-five cases reported in the literature,[10,11] averaging about three pregnancies each, seven died during pregnancy or soon after delivery, and ten of the surviving patients were definitely made worse by the pregnancy. The deaths resulted from ruptured aorta in four instances and from bacterial endocarditis, heart failure, and cerebral accidents in one instance each. These risks occur outside pregnancy, but pregnancy and labor add to the stress on the already strained aorta and cerebral vessels. Mendelson's unfortunate experiences[12] with three cases of coarctation of the aorta led him to interdict pregnancy for such patients. In contrast are the more favorable experiences reported by Baber and Daley[10] and those we are now reporting.

Toxemia developed in only one of our five patients with coarctation of the aorta. A larger series will be needed to evaluate this danger as well as to explain the intriguing phenomenon of change in blood pressure in pregnancy in these individuals. Cesarean section was not done in our group with coarctation, and the described complications did not occur. It would seem logical that, in view of the mortality reported, advice against pregnancy be given those with coarctation and that, if pregnancy does occur and advances, delivery by cesarean section would relieve the blood pressure elevations related to labor and benefit the patient.

The only cesarean sections in our entire series were for obstetrical reasons, and these were performed without untoward effects on patients without heart failure. Like Lund, we have gathered the impression that precipitous delivery occurs rather frequently in these patients. In fact, notes on several obstetrical records indicate that delivery occurred while the recommended forceps were being prepared. It would seem that a closer watch over these patients to insure a controlled emptying of the uterus would be wise. Hamilton has, and we believe with good justification, warned against sudden emptying of the uterus in any pregnant cardiac patient.

Our group as a whole does not bear out Lund's finding of a higher incidence of toxemia in congenital heart disease. Of our eighty pregnancies ten were accompanied by toxemia, representing four different patients, a rate of 12 per cent and a figure less alarming than the 33 per cent rate reported by Lund. The general incidence of toxemia in this hospital is 14.5 per cent. It is known that in toxemia the drop in blood pressure following delivery may, at times, reach collapse levels and in the presence of arteriovenous shunts may accentuate the hazard described by Hamilton. It may be that the infrequency of toxemia in our patients with shunts is partially responsible for the freedom of our group from such hazards. In the one instance in which collapse appeared, toxemia was present. Our fatality occurred in a patient who became decompensated because of severe toxemia, and it would seem well to exert special effort to prevent toxemia in these patients.

In general, the paucity of patients in each specific group prevents generalization. Suffice it to say that our groups with patent ductus arteriosus and coarctation of the aorta fared better than those of Lund and Mendelson, respectively.

In congenital heart disease in pregnancy, as well as in other types, the development of congestive failure is of great concern. A tendency to deterioration in cardiac classification early in pregnancy, to herald a progressive decline as noted by Lund, was not seen in this series. Only four of our patients had a history of failure before pregnancy or in a previous pregnancy, and they did remarkably well, but this number is far too small to warrant a disregard of Hamilton's warning concerning this group. Ideally, they should not be allowed to become pregnant, and pregnancy should be interrupted early if it occurs. Our series does not contain enough patients in the older age group to justify comment on this factor.

Despite the fact that twenty-one of our twenty-five patients with enlarged hearts were able to go through pregnancy without further failure, generalizations are not in order. The determination of right-sided cardiac enlargement is not an easy task, especially in pregnancy, and the criteria are less reliable in patients with many types of congenital heart disease. Similarly, symptoms and physical findings in these patients call for even more careful evaluation than in other pregnant cardiac patients.[8]

Cyanosis occurred in only two patients of this series, both with tetralogy of Fallot. One of these patients died, as stated previously; the other developed subacute bacterial endocarditis in the second trimester and responded satisfactorily to treatment. In general, cyanosis is considered an unfavorable sign in proportion to its degree and persistence and, when marked, has been considered a contraindication to pregnancy. Our present experience includes only two such patients, and neither did well. The hazard of bacterial endocarditis in pregnancy and the puerperium for patients with congenital heart disease is a real one.[13] Because of this, prophylactic antibiotics were frequently used in our patients.

Until sufficient data are compiled from the literature, it would seem wise, in the management of congenital heart disease in pregnancy, to follow the dictum of previous authorities regarding heart disease in general in pregnancy. De-

viation from these dicta may be considered in decisions as to cesarean section in patients with coarctation of the aorta. Special care should be taken to prevent toxemia. The prevention of precipitous parturition would seem wise. The use of penicillin prophylactically at the time of delivery to forestall the development of bacterial endocarditis is strongly urged.

SUMMARY AND CONCLUSIONS

A series of eighty pregnancies in thirty-three patients with congenital heart disease is reported. Four patients developed congestive heart failure as the result of pregnancy, and one death is recorded. The need for further reports is indicated. Until such reports are compiled, it is well to adhere in general to the established principles in the management of heart disease in pregnancy.

Special considerations include (1) prevention of toxemia, (2) avoidance of precipitous delivery, (3) early detection of vascular collapse, (4) cesarean section for patients with coarctation of the aorta, (5) prophylactic use of penicillin at labor, and (6) the use of newer diagnostic techniques in the study of these patients.

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A NEW ELECTROCARDIOGRAPHIC LIMB ELECTRODE

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WITH the introduction of direct-writing electrocardiographs, the technique has been simplified to such a degree that fastening of the limb electrodes by means of rubber strips takes now an appreciable proportion of the time of taking an electrocardiogram.

Fig. 1.—Oblique view of electrode.

The new electrode (Fig. 1) is mounted on a steel blade spring. The aperture between the upper and lower sides of the blade is 1¾ inches. This size will fit most adults and can be used for the arms as well as the legs. A smaller size should be used for children. The electrode is slipped over the limb at a level which is the most suitable for the individual thickness and held in place by means of the spring. The level of the limb at which the electrode is placed is irrelevant for the electrocardiogram. The time for fastening the spring electrode was found to be reduced by about 50 per cent, as compared to rubber strip fastening. The steel blade is also easier to clean than the rubber strips.

From the Veterans Administration Hospital and the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis.

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Conventional electrocardiographic electrodes are screwed (or soldered) to the upper blade; the electrodes may be sawed in half for this purpose. The steel blade was made from pants clips used by bicyclists ($0.05 apiece).

SUMMARY

A new electrocardiographic electrode is described which replaces the rubber strip fastening by a spring blade.

Clinical Reports

TEMPORAL ARTERITIS OCCURRING IN A NEGRO

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HINES, ILL.

IN 1932, Horton, Magath, and Brown[15] reported two cases of what they considered a disease entity, characterized by severe headaches, inflamed tender temporal arteries, anemia, and persistent mild pyrexia. Since that time, there have been well over fifty cases reported which fall readily within this clinical group. The term temporal arteritis or craniotemporal arteritis has proved most acceptable.

The age incidence varies between 55 and 80 years with a mean age of approximately 66 years, no patients falling outside this age group. Women predominate in a ratio of two to one. Until the present patient, all reported patients have been of the white race.

In one-half of the reported patients the appearance of temporal artery swelling and pain was preceded by a period, varying from one month to as much as thirty months, during which the patient suffered with weight loss, anorexia, generalized muscular and joint pains, fever, and night sweats. Headache was a constant feature, usually generalized at first, but localized in the temporal areas as signs of temporal artery involvement became prominent. Temporomandibular joint pain was present in eleven patients. Symptoms suggestive of generalized arterial involvement of the cerebral vessels, including epilepsy, transient loss of hearing, headaches, vomiting, papilledema, disorientation, coma, and mental sluggishness, were reported in eleven patients. In one-half of the patients there were ocular symptoms including partial and total blindness, photophobia, pain in the eyes, blurring of vision, and transient diplopia.

The most typical symptom of the entire complex is transient arteritis of the temporal arteries. This may last anywhere from a few weeks to several months. The artery is tender and enlarged, and the skin is reddened along its course at the onset; pulsations are lost. With subsidence of the inflammatory process, a cordlike enlargement with tenderness may persist for months, and pulsations may return. Occasionally, erosion of the skin and scalp have occurred. Enlarged cervical glands have been noted. Enlargement of the occipital artery with local induration and tenderness is not uncommon. There are a few reports

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of other involvements of the peripheral arteries including the radial, axillary, and coronary arteries. Intermittent claudication was present in six patients.

Fever is a common and practically constant finding. Maximum temperatures were 103° F. with an average of 100° F. The blood pressure was elevated in one-third of the patients. The pulse pressure, however, was high (over 60 mm. in one-half of the patients). Involvement of the ocular fundus was noted in one-half of the reported patients. Funduscopic findings were of two general types: (1) those usually associated with advanced arteriosclerosis including localized nerve atrophy, hemorrhages, exudates, silver and copper wiring and (2) closure of the central artery. Papilledema likewise was found, being assumed to be due to ischemia and edema of the discs.

The characteristic pathology of this clinical state is distinctive, but the variations make definite histopathological differentiation difficult. The characteristic picture has been that of round-cell infiltration, probably starting in the adventitia and spreading to all coats, accompanied by focal necrosis of the arterial wall and thrombosis of the lumen. Giant cells are frequently found in the arterial wall, especially in the older processes. Thirty-two biopsies have been reported. Seventy per cent revealed the typical pictures already mentioned, including giant cells; 20 per cent showed the same process, but giant cells were absent. Ten per cent of those reported revealed polymorphonuclear and eosinophilic infiltration not distinguishable from periarteritis nodosa.

Moderate anemia with slight leucocytosis has been a constant finding. Serology was consistently negative in the reported patients. Electrocardiograms were within normal limits. Spinal fluid examination revealed increased protein in one patient. Sternal marrows were not reported. Cultures in the majority of instances were sterile. However, in Horton and Magath's original cases actinomyces were found. *Staphylococcus aureus*, *Streptococcus viridans*, and gram-negative cocci were reported.

Treatment has consisted of removal, salicylates, iodides, Azosulfamide, sulfanilamide, vitamin concentrates, liver, papaverine, sulfathiazole, nicotinic acid, and amyl nitrite. Of the above-listed therapy, only removal has been followed consistently by any result. This has consisted of rapid relief of pain in the involved area and rapid disappearance of headache.

CASE REPORT

The patient, K. G., a 59-year-old Negro laborer, was admitted to the Veterans Administration Hospital, Hines, Ill., on Oct. 13, 1948. He had been well until two months prior to admission, when he developed sharp, intermittent, occipital pain which did not radiate. The pain was relieved by aspirin. Five days prior to admission, he developed tender areas in both temporal arteries. Definite swelling was noted in these areas by the patient. No history of visual disturbances, cardiovascular symptoms, or fever was obtainable. The past history, however, revealed that he had had syphilis in 1920, for which he had received arsenical treatment.

Examination on admission revealed a well-developed, well-nourished, Negro man who did not appear acutely ill. Tortuous, indurated, tender, temporal arteries were present bilaterally. Funduscopic examination revealed moderate arteriovenous nicking but no other abnormalities. The blood pressure was 150/100 mm. Hg. The heart was slightly enlarged, but no murmurs were present. No significant lymphadenopathy was present. Neurological examination was normal.

The first Wassermann and Kahn tests were negative. The second tests showed 1 plus Kahn and Wassermann negative, and a third test revealed a quantitative Kahn of 1 unit. Spinal fluid examination revealed two cells, 69.8 mg. per cent of sugar, total protein of 38 mg. per cent, 25 per cent Wassermann, and a gold curve 0012211000. The red blood cell count was 4,020,000, white blood cell count 7,100, hemoglobin 11 Gm., and platelets 298,000. The sedimentation rate was 28 and 25 mm. in one hour (Westergren). A tuberculin test, first strength, was positive. A brucellergin skin test was negative. Nonprotein nitrogen was 34.1 mg. per cent. Prothrombin time was 15 seconds (normal, 13 seconds). Fasting blood sugar was 134 mg. per cent. Multiple liver function tests were normal. Agglutinations for typhoid, paratyphoid A and B, proteus 0 × 19, *Brucella melitensis*, and *Brucella suis* were negative. An electrocardiogram showed left axis deviation with left ventricular strain. Visual fields were normal. Sternal marrow and electroencephalogram were normal.

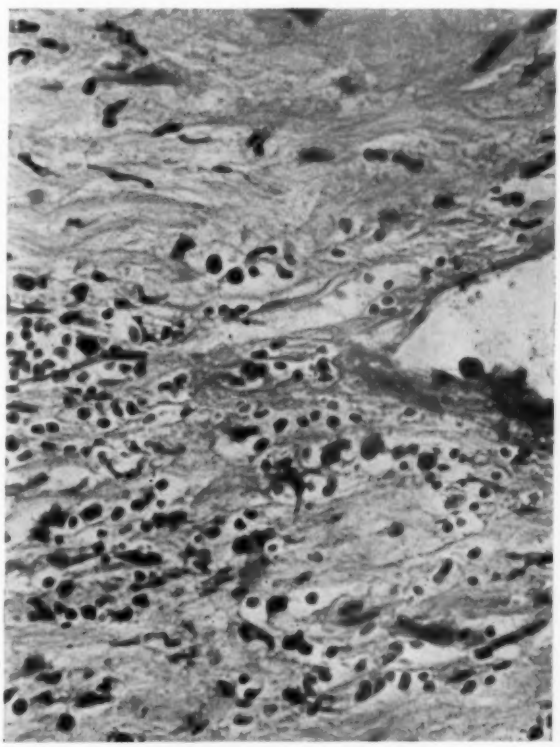

Fig. 1.—Microphotograph of the left temporal artery showing thickening of all layers, particularly the intima and media. Some early calcification. Infiltration with round cells resembling lymphocytes (× 430).

Biopsy of the left temporal artery was performed. Microscopic examination revealed thickening of all coats, particularly the intima and media (Fig. 1). The wall showed some evidence of early calcification. One section revealed infiltration with small round cells resembling lymphocytes. No plasma cells, eosinophils, leucocytes, or giant cells were seen.

Hospital Course.—During his hospital stay, the patient had a daily elevation of temperature to 99.8° F. Severe headaches persisted until the time of biopsy of the left temporal artery, at which time pain disappeared immediately from the left but persisted over the right artery. The right artery was not severed. The patient was discharged four weeks after admission. He was asymptomatic save for minor right temporal pain. Initially, the pain had been most severe on the left side, and the patient tolerated well the residual discomfort in the right temporal area.

Follow-up Studies.—The patient has been followed monthly for one year. Right temporal artery pain gradually subsided in one month. Two months after biopsy, he developed exertional dyspnea and precordial pain radiating down the left arm. Cardiac enlargement was demonstrated roentgenologically, and a coronary insufficiency pattern was present on the electrocardiogram. The patient was temporarily relieved of symptoms by papaverine 1½ gr. orally four times a day and nitroglycerin occasionally. One month later the symptoms had subsided and have not recurred. The electrocardiogram now suggested a left heart strain pattern as before and has since remained stationary.

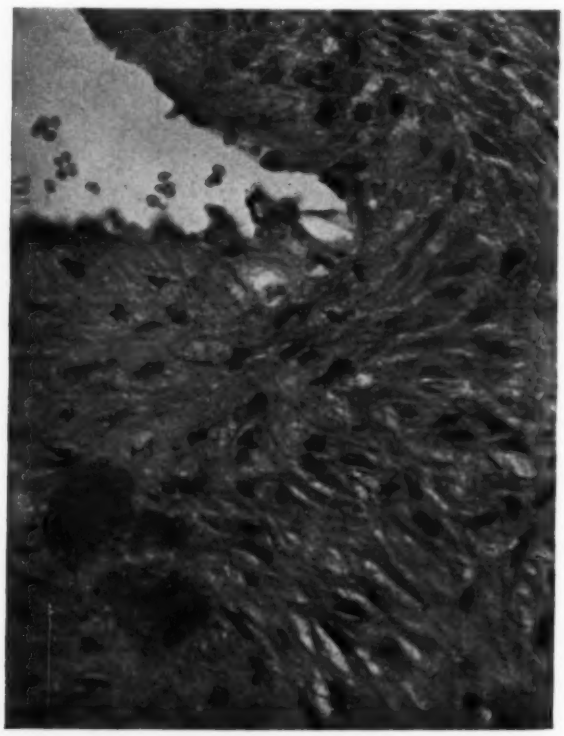

Fig. 2.—Microphotograph of the right temporal artery. Pronounced thickening of the wall with occasional infiltration with round cells and an occasional foreign body giant cell (× 430).

On Aug. 22, 1949, the patient returned with a recurrence of severe right temporal artery pain. Excision of this artery was followed by prompt relief of pain which has not recurred. Anemia persists as does a faintly positive serology and low-grade fever. Microscopic examination of the excised artery revealed thickening of all coats, particularly the intima and media, with infiltration of small round cells (Fig. 2). Scattered giant cells were seen. No calcification was present.

DISCUSSION

Forty-eight previous cases of temporal arteritis have been reviewed. Thirty-two of these patients had biopsies; the remaining sixteen were reported on a clinical basis. The patient in this report had a typical clinical course and typical physical findings. Biopsy was followed by prompt relief of symptoms on the side from which the biopsy was taken, but not on the opposite side. Subsequent biopsy of the opposite side for severe recurrent pain was likewise followed by

complete relief. Salicylates were of no effect in relieving symptoms, again demonstrating that biopsy is the treatment of choice where symptoms are prolonged or severe. Spontaneous regression is to be anticipated and may be awaited if symptoms are not too marked. A close association with generalized arteriosclerosis is again demonstrated. An infectious process is suggested by prolonged pyrexia, leucocytosis, and perhaps by the anemia. The finding of previous patients only in the white race is possibly because of a lack of a search for the disease in the Negro race and not because of a true lesser incidence of the disease.

This patient had a weakly positive blood and spinal fluid serology, apparently the residual of a previous syphilitic infection. That the arteritis was not due to syphilis we believe is demonstrated by the following facts: (1) a typical clinical course with pyrexia, temporal pain, and anemia, (2) response to biopsy, (3) spontaneous regression of the less severely involved artery without antisyphilitic therapy, and (4) the biopsy which did not resemble syphilitic arteritis even on serial sections.

SUMMARY

A case of temporal arteritis is presented. This is the first case reported in a member of the Negro race. The clinical course is characteristic with persistent low-grade fever, inflammation of the temporal arteries, and relief of pain by severance. The artery not severed apparently gave rise to persistent mild symptoms, with recurrence finally disappearing on section. The patient had a weakly positive serology on two occasions. He had an old history of syphilis. Definite arteriosclerotic changes are present in the patient including coronary insufficiency and funduscopic changes. The course was benign with complete subsidence of symptoms referable to temporal arteritis, but persistence of symptoms of moderate myocardial insufficiency and coronary artery disease, suggesting involvement of multiple arteries. The pathological picture of the arteries in this patient demonstrated round-cell infiltration of all layers with thickening, particularly of the intima and media. No eosinophilic or polymorphonuclear leucocytes were present. Scattered giant cells were detected.

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IDIOPATHIC CARDIAC HYPERTROPHY IN ADULTS

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AT THE turn of the century "idiopathic cardiac hypertrophy" of the adult heart was a diagnosis widely made. As knowledge of the etiology and pathogenesis of cardiac disease evolved, the term gradually fell into disrepute and now is restricted to a polyglot of conditions, characterized primarily by myocardial hypertrophy for which no definite cause is demonstrable. Cases present likewise one or more of the following features: symptoms of cardiac insufficiency with a rapidly downhill course, various types of arrhythmia, emboli to the pulmonary and systemic circulations, and death from increasing cardiac failure or sudden death.[1,2,3,4] The relative paucity of the literature dealing with idiopathic cardiac hypertrophy is the main reason for this report.

CASE REPORT

A. E. D., a 34-year-old white man, married, was first examined Oct. 2, 1944. Following severe exertion in a hurricane Sept. 14, 1944, occasioned by his work as a telephone test cable man, he had developed sudden palpitation. He continued to work steadily in spite of increasing dyspnea. During the week before examination a sensation of substernal oppression was induced by walking, with relief only by rest of two or three minutes. He was also awakened during this week by attacks of nocturnal dyspnea. A sore throat developed Oct. 1, 1944, as well as paroxysms of cough. He had lost twelve pounds during the last two months, following separation from his wife. The history otherwise was negative. The last thorough physical examination in 1942 had been normal.

The past medical history was negative except for measles and mumps during childhood. His father had died of pulmonary tuberculosis. His mother died during her second pregnancy. A brother died of cardiac failure at the age of 13 years (etiology unknown). The patient had always enjoyed good health. He used tobacco and alcohol in moderation.

Physical examination disclosed a young, well-developed adult of medium height. There was marked pallor of the face. Cyanosis was absent. The weight was 149 pounds (normal, 160 pounds), the temperature 100.3° F., and the apical pulse rate 180 per minute and regular. The pulse was not palpable at the wrist. The blood pressure was 80 mm. Hg systolic; the diastolic blood pressure was not obtainable. The thyroid gland was not palpable. The lungs were clear, and the remainder of the physical examination was normal.

The electrocardiogram (Fig. 1) showed supraventricular paroxysmal tachycardia. Pressure over the eyeballs and the carotid sinus was ineffective. Treatment was begun with quinidine sulfate, 0.3 Gm. every four hours. After four doses the pulse rate was 130 per minute, regular, perceptible at the wrist, and gradually stronger in volume. Quinidine therapy was continued every six hours and was discontinued after the pulse rate fell to 120 per minute. Coarse crackles were audible at the base of the right lung. On Oct. 4, 1944, the patient felt fairly well except for severe nausea. At this time the pulse rate was 116 per minute and regular. The radial pulse

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was feeble. The blood pressure was 80/68 mm. Hg. Dyspnea increased, slight cyanosis of the lips and fingernail beds appeared, and numerous moist râles were heard at both lung bases. The liver was now enlarged 5 cm. below the costal margin in the mid-clavicular line and was very tender. Slight pitting edema of the extremities was present.

In view of the increasing cardiac decompensation, it was deemed advisable to hospitalize the patient (Oct. 5, 1944). An electrocardiogram (Fig. 2) taken at this time showed sinus tachycardia (cardiac rate 115 per minute), left bundle branch defect, myocardial damage, and possible quinidine effects. The temperature ranged between 98.0° and 99.4° F. and the pulse rate between 100 and 110 per minute on October 5 and October 6, gradually rising to 140 per minute. The blood count showed hemoglobin 9.3 Gm., red blood cells 3,200,000 per cubic millimeter, and the white blood cells 10,100 per cubic millimeter with 79 per cent polymorphonuclears and 21 per cent lymphocytes. The following day, the white blood cell count was 10,800 per cubic millimeter with 84 per cent polymorphonuclears and 16 per cent lymphocytes.

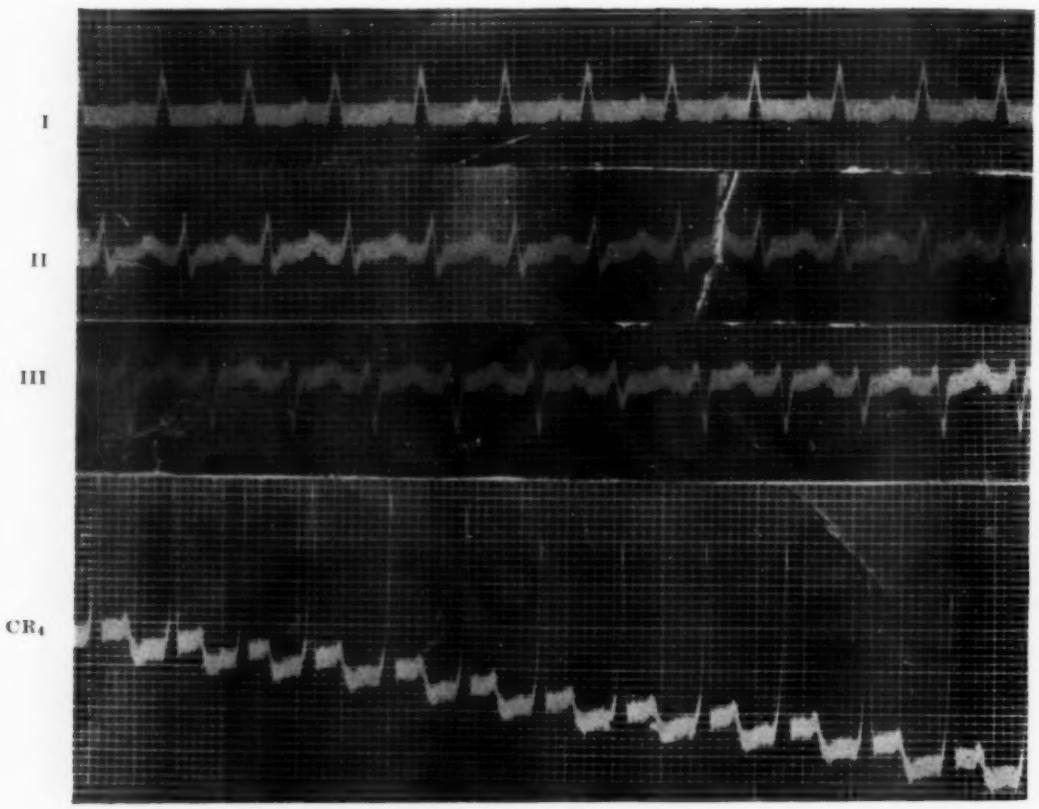

Fig. 1.—The cardiac rate is 186 and regular. P waves are absent. The QRS complex is slurred, with low voltage in the limb leads, upright in I and II and inverted in III and CR_4; the duration is 0.06 second. The electrocardiographic diagnosis on Oct. 2, 1944 was: supraventricular paroxysmal tachycardia.

The patient was put in an oxygen tent, and treatment was instituted with digitalis powder, 1½ gr. every three hours. The tachycardia (pulse rate 140 per minute) persisted, extrasystoles developed, and cyanosis became more marked. Coupled with the failure to respond to digitalization, the question of underlying hyperthyroidism was raised Oct. 7, 1944, and treatment with Lugol's solution was begun empirically. During the succeeding two days the patient seemed to improve clinically; the cardiac rate was 120 per minute, the radial pulse volume was good, the dyspnea and cyanosis lessened, and the patient felt stronger. An electrocardiogram (Fig. 3),

taken late on Oct. 7, 1944, showed findings suggestive of anteroposterior infarction. On Oct. 9, 1944, he developed sudden restlessness, cyanosis increased rapidly, the pulse became imperceptible, and the patient died.

Autopsy.—The autopsy disclosed the body to be that of a well-developed young adult man. There was moderate cyanosis of the lips and fingers. Herpes labialis was present.

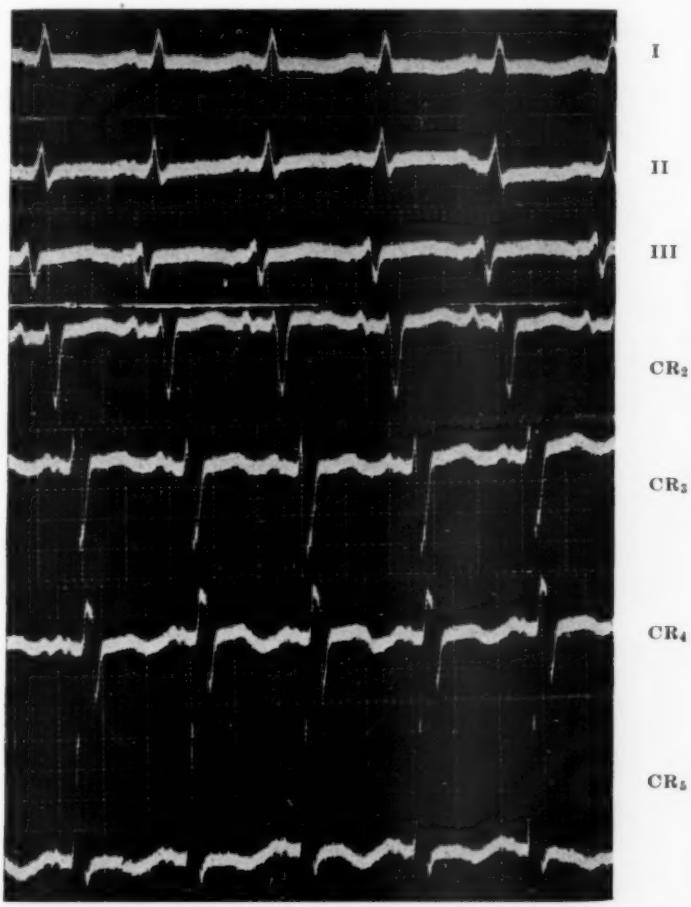

Fig. 2.—The cardiac rate is 115. Sinus rhythm is regular. P waves are bifurcated. There is a P-R interval of 0.12 second. The QRS complex is slurred, with a duration of 0.10 second, and splintered. The S-T interval is normal. The T waves are inverted in I and CR_5 and low in others. The electrocardiographic diagnosis on Oct. 5, 1944 was: simple tachycardia, left bundle branch defect, myocardial damage, and quinidine effects (?).

Serous Cavities: There were 250 c.c. of straw-colored fluid in the right chest, 150 c.c. in the left chest, and about 300 c.c. in the abdomen.

Heart: The heart weighed 490 grams. There was marked dilatation of all chambers with concomitant widening of the mitral and tricuspid rings. The chamber walls were within normal limits of thickness.* The valves and coronary vessels were normal. The myocardial fibers showed slight hypertrophy.

***As White[20] has pointed out, the thickness of the ventricular walls is a very inadequate way to express relative size or weight of the ventricles and "the mere measurement of the . . . ventricular wall thickness might be the normal expected for an undilated ventricle and so enlargement might be overlooked."**

Liver: The liver weighed 2,000 grams. A nutmeg pattern, together with fatty degeneration, was exceedingly prominent in all sections.

Lungs: The lungs were large. Each lobe showed massive edema. In addition, each lower lobe showed a number of dark reddish-purple, wedge-shaped areas of firm tissue. One of these, in the right base, occupied about one quarter of the lung tissue.

Miscellaneous: The spleen, adrenal glands, and thyroid gland were normal grossly and histologically. The kidneys were normal except for a small infarct.

Pathological Diagnosis: Idiopathic cardiac hypertrophy and dilatation, pulmonary edema, and multiple pulmonary infarctions.

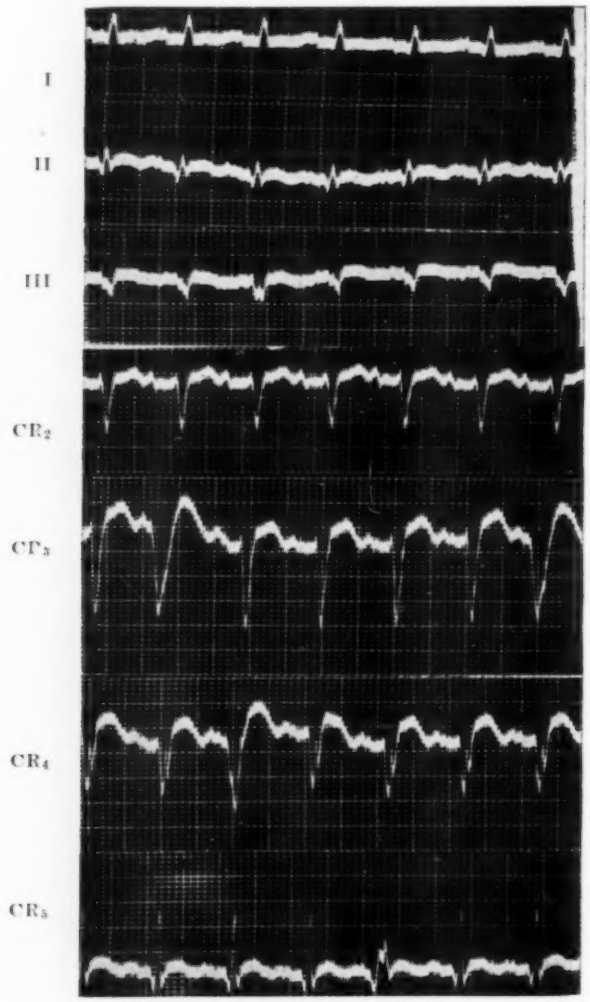

Fig. 3.—The cardiac rate is 143. There is sinus rhythm with occasional ventricular extrasystoles. The P waves are split. There is a P-R interval of 0.16 second. The QRS complex is slurred with a low voltage in the limb leads: R is very small in CR_2, CR_3, and CR_4. The S-T interval is elevated in II, III, CR_2, CR_4, and CR_5. The T waves are flat in II, inverted in III, and diphasic in CR_4 and CR_5. The electrocardiographic diagnosis on Oct. 7, 1944 was: simple tachycardia with occasional ventricular extrasystoles. The tracing indicates infarction, both anterior and posterior.

COMMENT

The present case is that of a young adult man whose progressive cardiac failure was ushered in by a cardiac arrhythmia and who died suddenly. Postmortem examination revealed essentially cardiac hypertrophy and dilatation with nothing tangible as to etiology. The chief presenting symptom was dyspnea on exertion, as is commonly the case.[5] In only two patients has cardiac pain been the presenting symptom.[1,6] Occasionally, palpitation is the first complaint.[7] A few cases have been accompanied by a slight elevation of temperature. In some the cause may have been pulmonary infarction,[5] in one, a tracheitis.[2] In one patient, a boy of 14 years, the course closely simulated acute rheumatic fever[8]; in others the cause of the pyrexia remained obscure. The present case had pyrexia that may possibly be linked to a grippelike infection.

Cardiac arrhythmias, especially paroxysmal tachycardias, are not uncommon.[7] Two of Levy and Rousselot's patients had past attacks[7]; the present subject's attack apparently initiated his illness. Auricular fibrillation, both paroxysmal and permanent,[5,9,10,11] paroxysmal auricular flutter,[5] and partial[7] and complete heart block[4,5,9] have been reported. Other electrocardiographic changes are common, being minor in most cases unless cardiac fibrosis is advanced.[5] Sinus tachycardia of unexplained origin is a prominent feature in several of the reported cases.[5,8] In the present case the initiating paroxysmal tachycardia responded to quinidine. The ensuing sinus tachycardia developed into what appeared electrocardiographically to be an associated acute coronary thrombosis. This was not substantiated at autopsy.

Frequently, embolism, chiefly pulmonary, is present, apparently from mural thrombi.[1,5,7] The mural thrombi do not necessarily have underlying endocardial pathology.[5] Advanced sclerosis of the coronary arteries is conspicuously absent,[5] and generalized arteriolar sclerosis also is not present.[5,9,12] Many patients have repeated bouts of cardiac failure.[5,7,9] The duration of life after the onset of symptoms is variable, from two months to several years.[8] In a few cases there are no premonitory symptoms, with death occurring suddenly.[1,2,3,5]

The pathological changes in the heart vary greatly. In a few cases cardiac hypertrophy alone is present.[3,9] Many patients present also marked endocardial and subendocardial fibrosis[5-10,13] and even areas of necrosis and myocardial fibrosis.[5,8,9,10] The question has even been raised as to whether hypertrophy of the muscle fibers is really a requisite. Some evidence has been adduced to the contrary.[8,14]

Numerous hypotheses have been advanced to explain the pathogenesis. Deficiency of vitamin B was considered the causative agent in Dock's[16] and Smith and Furth's cases,[10] but further evidence seems to render this view untenable.[16] Similar cardiac lesions have been produced in rats fed on potassium deficient diets.[17] Flynn and Mann[13] think that circulatory stasis consequent to congestive heart failure produces inadequate oxygenation and nutrition of the subendocardial tissue with consequent hydropic degeneration, necrosis, and fibrosis of the subendocardial tissue. Mural thrombi and thrombosis of the Thebesian veins in the involved areas may then develop. The question of von

Gierke's glycogen storage disease[18] has been considered, but it obviously does not fit the picture. The possible etiological role of strenuous exercise has been raised in some cases.[1,2] One remarkable patient was an outstanding English athlete, 78 years old, who died suddenly and presented the typical picture of idiopathic cardiac hypertrophy at autopsy.[19] Although the role of exercise in the production of enlarged hearts is not accepted by most cardiologists, there is evidence that such a factor may operate in rare cases.[20] Fiedler's myocarditis[21,22] does not fit the pathological picture except in a few cases.[10] The role of hypertension has received new emphasis recently.[5,20,23] The maximum and minimum blood pressures may lie within normal limits, but the mean dynamic pressure, as determined by an oscillometric method, may be elevated and thus play a role in the pathogenesis of cardiac hypertrophy. Recent observations tend to indicate a much wider incidence of this special form of hypertension than was formerly believed to be the case. A history has been elicited in several instances of idiopathic cardiac hypertrophy strongly suggestive of a familial tendency to the disease, especially in men.[4] In the present instance the sole brother died of cardiac failure of unknown etiology at the age of 13 years.

The question has been posed as to whether the cases described in the literature represent a single disease picture observed at different stages or whether they are of heterogeneous origin.[5,24] It is possible that the case described in this paper represents an early stage of the disease. Had he not died in the first bout of decompensation, he might have gone through several episodes of cardiac failure[9] and ultimately developed the full-blown picture of the disease.

SUMMARY

1. A 34-year-old white man developed a supraventricular paroxysmal tachycardia of two and one-half weeks duration, with response to quinidine therapy. Progressive cardiac failure ensued, terminating with electrocardiographic evidence of myocardial infarction and followed by sudden death. Autopsy disclosed simply idiopathic cardiac hypertrophy and dilatation.

2. A brief review of the literature is incorporated.

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MULTIFOCAL VENTRICULAR TACHYCARDIA INDUCED BY ETAMON IN A CASE OF PHEOCHROMOCYTOMA

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PHEOCHROMOCYTOMAS (tumors of adrenal chromaffin tissue) have recently been considered with renewed interest because of the development of adrenergic blocking agents such as N, N-Dibenzyl-beta-chloroethylamine (dibenamine), benzazoline hydrochloride (Priscoline), the benzodioxanes, and dihydroergocornine. The case to be described was typical of the paroxysmal hypertension produced by these tumors. The electrocardiographic record of a hypertensive episode and the remarkable control of the hypertension and arrhythmia by medication are of interest.

CASE REPORT

W. C., a 26-year-old white man, entered the Veterans Administration Hospital on June 20, 1949, complaining of transient weak spells, occurring for one year. The attacks were characterized by a period of weakness which lasted two minutes, followed by a "knotting" sensation in the epigastrium, pounding of the heart and temples, and, finally, trembling of three to five minutes' duration. He noticed shortness of breath during some of the attacks and vomited on one occasion. These symptoms occurred about once a week and were initiated by activity such as bending and lifting. He made the observation that he seemed to recover more rapidly if he continued to work. He visited his doctor on two occasions and was told that his blood pressure was elevated on one occasion and normal on the other.

Past history revealed a head injury in 1934, when he coasted over a bluff on a sled. He had since been troubled with a severe, pounding, expanding headache which sometimes affected the nuchal region. The headaches occurred at weekly intervals but were independent of, and seemed to diminish after, the onset of the weak spells.

On physical examination he was a tall, slim, well-developed, well-nourished, relaxed white man demonstrating no physical abnormalities. Blood pressure was 110/60 mm. Hg with a pulse rate of 66.

Laboratory Studies.—Blood cell count, serology, and urinalysis were normal. The urine concentrated to a specific gravity of 1.027. Basal metabolic rates were +26 and +4. An oral dextrose tolerance curve was: fasting 92 mg. per cent, 30 minutes 137 mg. per cent, 1 hour 96 mg. per cent, 2 hours 78 mg. per cent, and 3 hours 84 mg. per cent. One isolated fasting blood dextrose determination was 145 mg. per cent.

Radiograms demonstrated a normal chest. Abdominal roentgenograms gave good delineation of the left kidney, but the right was indefinite. An intravenous pyelogram was normal, but there was a suggestion of a depression on the upper pole of the right kidney. Laminagrams also suggested a radiopacity above the right kidney.

From the Veterans Administration Hospital, Portland.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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Hospital Course.—The patient received 0.05 mg. of histamine base intravenously while being examined for entrance into the hospital and promptly developed a systolic blood pressure of 230 mm. Hg. His cold pressor test was normal. He then received 0.05 mg. of histamine base intravenously while an electrocardiogram was being taken, but he developed no significant rise

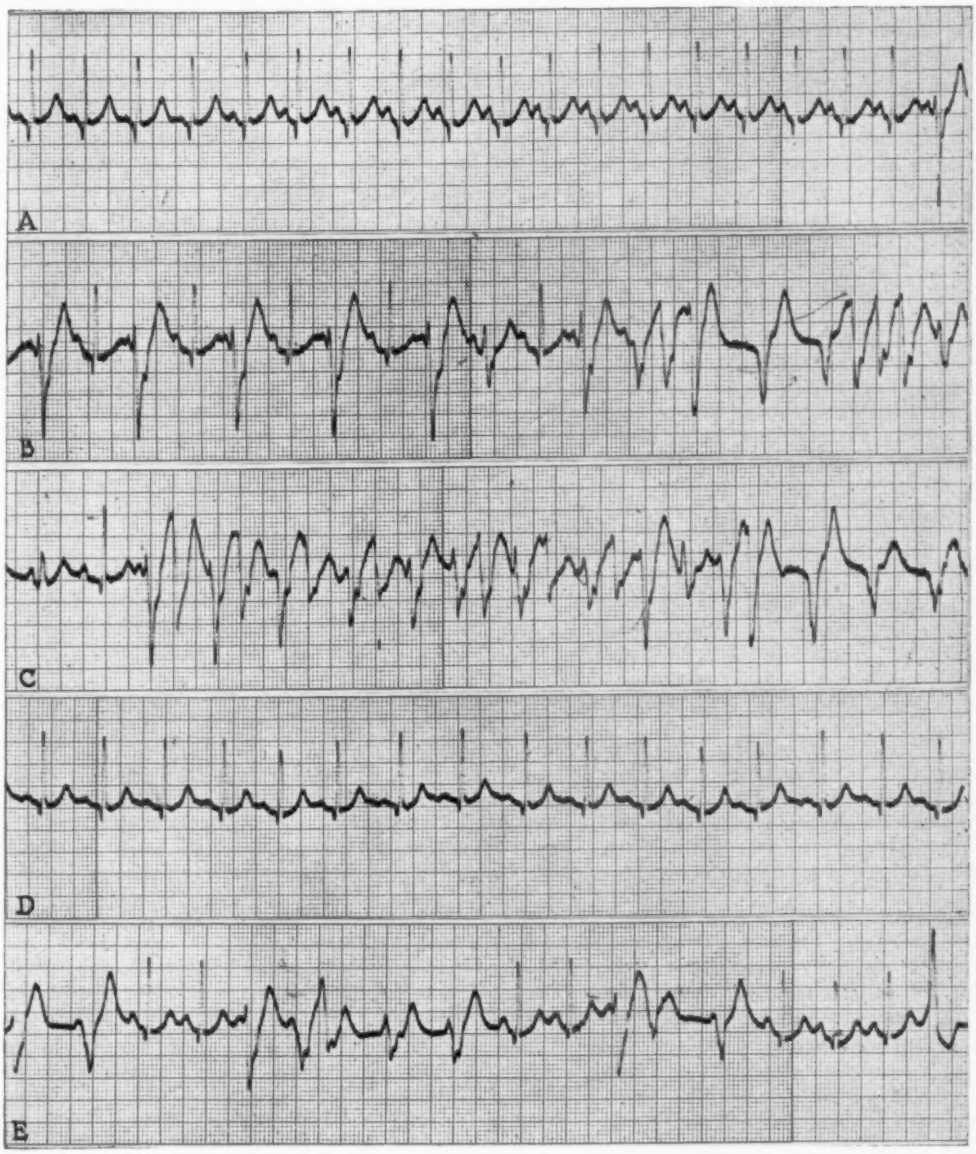

Fig. 1.—Reproductions from a continuous electrocardiogram (Lead II) obtained during a hypertensive crisis induced in a patient with a pheochromocytoma by intravenous administration of 300 mg. of Etamon. See Fig. 2 for the timing of the electrocardiographic tracings represented. *A*, Immediately after administration of Etamon. *B*, Six seconds after *A*. Many ventricular ectopic beats occurred as bigeminy and then as a series from varied foci. The P waves were regular at a rate of 140. *C*, P waves could no longer be identified, and the series of ectopic ventricular systoles attained rates of about 210. *D*, Following aminophylline, the rhythm became regular. *E*, Recurrence of ventricular ectopic beats.

in blood pressure. On the following day the test was repeated with almost identical results. The pressure, when recorded at thirty-second intervals, was 130/70, 120/30, 110/80, 160/100, 160/90, 150/95, and 140/80 mm. Hg. Ten minutes after the histamine was given, 300 mg. of Etamon (tetraethylammonium chloride) were administered intravenously (Fig. 2). The first blood pressure, obtained thirty seconds after the drug was administered, was 220/130 mm. Hg. At this time the patient noticed that his hands and feet were tingling. He became very restless, his pupils were widely dilated, and he developed a pounding headache that was more severe than any of his former headaches. The blood pressure thirty seconds later was 250/150 mm. Hg, and the electrocardiogram (see Fig. 1) unexpectedly showed rapid multifocal ventricular extrasystoles. The patient became frightened, had an intense desire for activity, and was allowed to assume a semierect position, but the pressure remained elevated at 220/140 mm. Hg. Two minutes after the Etamon administration it was still 220/120 mm. Hg, and the alarming rhythm was

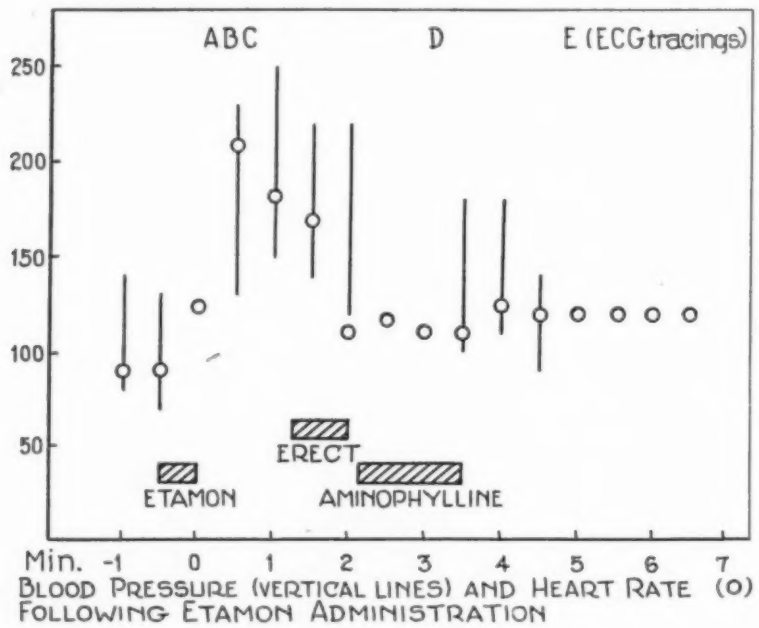

Fig. 2.—Blood pressure and heart rate during a hypertensive crisis in a patient with pheochromocytoma induced by Etamon. The letters *A*, *B*, *C*, *D*, and *E* refer to the time of the illustrated electrocardiograms in Fig. 1.

still noted on the electrocardiogram. There was some slight improvement in the rhythm on standing, but the patient complained so bitterly of his headache that he was again placed in a supine position and 250 mg. of aminophylline were administered intravenously, which resulted in a regular rhythm for about one minute. The blood pressure dropped to 180/100 mm. Hg just after the drug was administered and remained in that range for thirty seconds when it declined to 140/90 mm. Hg. No further elevations of pressure were noted. The electrocardiogram, however, continued to show runs of ventricular tachycardia and ectopic beats for two minutes after the blood pressure returned to normal. The patient continued to have a severe headache and to feel very restless for eight hours.

Subsequently, surgical correction of the hypertension was recommended, but the patient insisted the operation be delayed two months. He was allowed to leave with the recommendation that he take 3 gr. of quinidine three times daily. He stopped the quinidine because of malaise and continued to have mild attacks of weakness at the usual rate of about once a week.

After his return to the hospital, vigorous massage of each suprarenal area did not produce a hypertensive response. A trial of dibenamine, 2 mg. per kilogram of body weight, was given, and after one hour he was placed in a standing position at his bedside, at which time his blood pressure fell from 120/80 to 80/60 mm. Hg in one minute with a concomitant rise in pulse rate from 70 to 120. When the patient was placed in a supine position, the blood pressure returned to 130/60 mm. Hg, and the pulse rate slowed to 60. A dose of 0.05 mg. of histamine base was administered intravenously and caused a fall in pressure to 80/40 mm. Hg and a tachycardia of 150. After ninety seconds the blood pressure reached 140/70 mm. Hg, and the patient noticed an unpleasant pulsating sensation in the mid-abdomen. Ten minutes later 300 mg. of Etamon were administered intravenously, and the pressure dropped from 130/60 mm. Hg with a pulse of 65 to 120/70 mm. Hg with a pulse of 115 in an interval of thirty seconds. No hypertension or arrhythmia could be induced.

The patient was prepared for operation by administering 200 mg. of quinidine four times daily, the last dose being given thirty minutes before operation. Dibenamine, 2 mg. per kilogram of body weight, was administered two hours before the scheduled time of operation. Morphine sulfate, 10 mg., and atropine sulfate, 0.4 mg., were also given preoperatively. Anesthesia was induced with Sodium Pentothal and maintained with curare and endotracheal nitrous oxide. A continuous drip of 0.2 per cent procaine hydrochloride was maintained during the operation.

The right adrenal gland was exposed through a posterior nephrectomy incision with resection of the eleventh rib. The peritoneal space was not entered. The adrenal gland appeared at first inspection to be normal in size, position, and color, but on palpation a firm mass was felt beneath it. During brief manipulation of the tumor the systolic blood pressure suddenly rose from 110 to 190 mm. Hg with an increase in pulse rate from 110 to 180. This subsided rapidly. The tumor was round, firm, gray, 3 cm. in diameter, covered with a thick capsule, and weighed 9.3 grams. It lay upon the inferior vena cava, displaced the adrenal gland forward and outward, and appeared to arise from the under surface of the lower third of the adrenal gland. Approximately one-third of the adrenal gland was removed with the tumor.

The rise of blood pressure to 190 mm. Hg during palpation of the tumor was the only sign that a pressor substance was being liberated. A direct recording electrocardiograph was used to observe the cardiac rhythm during the operation; it ran continuously, but strips were recorded intermittently. Lead II was observed except during the induction of anesthesia and the skin incision when electrical interference obliterated the record. Not one ectopic beat or other arrhythmia was noted.

The postoperative course was uneventful with the blood pressures varying from 110 to 140 mm. Hg systolic and 40 to 80 mm. Hg diastolic. The patient was discharged on the tenth postoperative day. Shortly after arriving home and while sitting in a chair, he experienced a pounding sensation in the area of his heart which lasted about thirty seconds. This was the only experience that resembled the preoperative complaint during a six-month observation period. The headache, which has been considered a separate problem, continued to occur about once or twice a month.

Studies performed six months postoperatively showed a blood cell count and urine examination without abnormality. The basal metabolic rate was −9. An oral dextrose tolerance curve was: fasting 96 mg. per cent, 149 mg. per cent in 30 minutes, 76 mg. per cent in 1 hour, 76 mg. per cent in 2 hours, and 96 mg. per cent in 3 hours. A cold pressor study was normal, and 0.05 mg. of histamine base followed ten minutes later by 300 mg. of Etamon administered intravenously no longer produced a significant hypertensive response. Electrocardiograms showed no abnormalities.

Histologic examination of the tumor revealed a syncytial mass of cells enclosed in a dense fibrous tissue capsule with moderately thick, irregular connective tissue septa. The cell membranes were seldom observed, and the cells contained numerous fine yellowish-brown granules. The nuclei were small, uniform in size, and contained no mitotic figures. A few small clumps of chromatin material were observed within the nuclei, and an occasional nucleolus was seen. The pathological diagnosis was pheochromocytoma, adherent to the right adrenal. The Physiology Department of the University of Oregon Medical School estimated an epinephrine equivalent of 3.9 mg. per gram on the basis of pressor responses in dogs given Nembutal.

DISCUSSION

Pheochromocytomas produce either a paroxysmal or sustained type of hypertension by the liberation of epinephrine and possibly nor-epinephrine. Bio-assays of tumor tissue following surgical removal have demonstrated concentrations of epinephrine equivalents varying between 0.12 and 20 mg. per gram.[3] The epinephrine release stimulates the heart by a direct effect on the myocardium and myocardial conduction tissue, causing acceleration of rate and frequently alteration of rhythm. The chief vascular action is constriction of the vessels of the skin, mucosa, abdominal viscera, cerebrum, and retina, and dilatation of the vessels of the skeletal and cardiac muscles. Because the net result is a decrease in the volume of the vascular bed and an increase in the cardiac output, an elevated blood pressure results.

It follows that deaths from pheochromocytomas are due to the liberation of epinephrine and resulting disturbances in cardiac rhythm or the production of vascular hypertension. The operative mortality has been variously reported from 16 per cent to 40 per cent.[2,4] These rather formidable figures emphasize the necessity for an adrenergic block during operation.

Dibenamine, in doses which are well within therapeutic levels, is capable of blocking the effects of epinephrine. It has been used in several cases of pheochromocytoma with good results[5,8,12] and has proved valuable in the diagnosis of the sustained type of hypertension due to pheochromocytoma. Because of the production of a satisfactory blocking action of 36 to 96 hours duration, it is the adrenergic blocking agent of choice. This allows a preoperative preparation of the patient with sufficient time to obtain a stabilized blood pressure without need for administration during the operation. The correct dose can be adequately determined by clinical trial before hand. It is the only adrenergic blocking agent known to be effective in preventing cardiac arrhythmias caused by epinephrine.[9]

The diagnosis of the present case was suspected in the admitting office by the history and effect of the intravenous administration of histamine. It is informative that two subsequent doses of histamine failed to produce the characteristic rise in pressure, but the administration of Etamon precipitated an attack ten minutes after histamine failed. The localization of the tumor was rather indefinite on the basis of radiographic findings, but it was aided by recent symptoms of pain on the right side of the back during the paroxysms and fortified by the fact that about 66 per cent of the tumors removed have been found on the right side.

The electrocardiogram (Fig. 1) is worthy of consideration. After the administration of Etamon the pulse increased to 130 beats per minute for fifteen seconds and bigeminy occurred for fifteen seconds. Following this, the rate and rhythm varied from runs of ventricular ectopic beats occurring from varied foci to ventricular tachycardia with rates up to 210 beats per minute. Areas in the tracing are indistinguishable from ventricular fibrillation, but probably represent multifocal ventricular tachycardia. This erratic rhythm continued for seventy seconds, until the patient was placed in an upright position in an

attempt to lower the blood pressure. This did not lower the pressure or reduce the symptoms, but the rhythm became regular for six seconds and then the frequent ventricular ectopic beats appeared for thirty seconds. At this time 250 mg. of aminophylline were administered, and the rhythm became normal for seventy seconds, only to break again into runs of ventricular tachycardia and ectopia for two minutes and twenty seconds before returning to a normal pattern.

It is believed the production of the paroxysm of hypertension and cardiac arrhythmia was due to liberation of epinephrine from the tumor. The epinephrine release in this case was induced by Etamon. In a "normal" individual an orthostatic hypotension results during the period when Etamon is acting. This has been attributed to the total autonomic blockade at ganglionic level and the failure of the normal orthostatic autonomic responses to become manifest. As the action of Etamon is chiefly at ganglionic levels and circulating epinephrine acts at the neuroeffector junction, the latter action will predominate, and an orthostatic hypotension could not occur as long as sufficient circulating epinephrine is present. Thus, in this case, the erect position of the patient failed to lower significantly the blood pressure because of epinephrine-induced vasoconstriction, an action that is peripheral to the autonomic ganglionic blockade of Etamon.

SUMMARY AND CONCLUSIONS

A case of paroxysmal hypertension due to pheochromocytoma is presented which demonstrates several cardiac manifestations. The following facts are revealed by this case:

1. Intravenous administration of histamine induced a paroxysm of hypertension in a patient with pheochromocytoma but failed to do so on two subsequent occasions.
2. Etamon probably initiated a paroxysm of hypertension in this patient after the histamine failed.
3. Transient multifocal ventricular tachycardia was recorded during the induced attack of paroxysmal hypertension.
4. Dibenamine prevented the hypertensive attacks from being initiated by either histamine or Etamon.
5. Dibenamine was apparently of benefit in moderating the hypertension and preventing cardiac arrhythmias during surgical manipulation and removal of a pheochromocytoma.

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A CASE OF TRANSPOSITION OF THE LARGE VESSELS IN AN ADULT WHO LIVED TO THE AGE OF 38 YEARS

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THE following case is reported because of the extreme rarity of transposition of the large vessels in adult life.

CASE REPORT

A. S., a 38-year-old Negro woman was admitted to the Medical Service of the Hospital for Joint Diseases directly from the Outpatient Department because of a fainting spell, which was followed by extreme cyanosis and dyspnea. Some degree of cyanosis had been present, as far as the patient knew, since her earliest infancy and had always been accentuated by moderate exertion. At 3 years of age she had experienced an episode similar to that preceding admission. Her parents were told at that time that she had heart disease. Partly on advice of physicians and partly by necessity, she had always restricted her activities. More than moderate exertion resulted in episodes of marked cyanosis and dyspnea associated with palpitation and sharp knife-like pains in the left chest. During the year prior to admission these attacks came on more frequently, were of increasing severity, and lasted a longer time. Twelve days before admission, while standing in the subway, she had an attack but, in addition, fainted. Again, nine days before admission, she experienced another episode with fainting on attempting to get out of bed. The third attack occurred in the Outpatient Department and resulted in her being admitted to the hospital. There was no history of orthopnea, nocturnal dyspnea, or edema. The patient was married and had been pregnant at the age of 23 years. She carried to term without any untoward symptoms and was delivered of a stillborn fetus. As far as could be determined by questioning the patient, she had no symptoms of congestive heart failure nor did her usual cyanosis and dyspnea increase in severity at the time.

Examination on admission revealed a dyspneic and cyanotic Negro woman who appeared much younger than her chronological age. There was definite curvature and cyanosis of the nails but no clubbing. The blood pressure was 100/60 mm. Hg, the respiration 28, and the heart rate 100 per minute. There was no evidence of congestive heart failure. The heart appeared to be slightly enlarged to the left. The apical impulse was diffuse and pounding, and the point of maximal impulse was found in the fourth intercostal space in the mid-clavicular line. No thrills were felt. The rhythm was regular. The P_2 was louder than the A_2. A moderately long, harsh, systolic murmur was heard with maximum intensity in the left third interspace and was transmitted all over the precordium. Funduscopic examination revealed marked hyperemia of the discs, dilated and tortous veins, but no arterial pulsations. The lungs were clear. The liver was felt two fingers below the costal margin, and the spleen was not palpable. There was no peripheral edema.

The patient was placed in an oxygen tent and improved within twenty-four hours. The day following admission, it was possible to fluoroscope her chest. This revealed minimal right ventricular and moderate left ventricular enlargement, a somewhat prominent pulmonary artery, and a normal aortic silhouette. Roentgenologic examination confirmed the fluoroscopic findings

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and showed a few fibrotic strands in the first left interspace(Fig.1). An electrocardiogram showed marked right axis deviation a deep S_1, low monophasic, slurred QRS_2, deep Q_3, low T_1, and depressed $S\text{-}T_2$ and $R\text{-}T_4$ (Fig. 2).

The other laboratory data were as follows: hemoglobin 21.4 Gm. (Sahli); erythrocytes 8,050,000; leucocytes 11,200 with 83 per cent segmented and 2 per cent nonsegmented polymorphonuclear leucocytes and 15 per cent lymphocytes. The blood sugar was 144 mg., the nonprotein nitrogen 28 mg. per cent. The total cholesterol was 166 mg. per cent with 29 per cent free cholesterol. The hematocrit was 74 per cent. The Kahn and Kline reactions were negative.

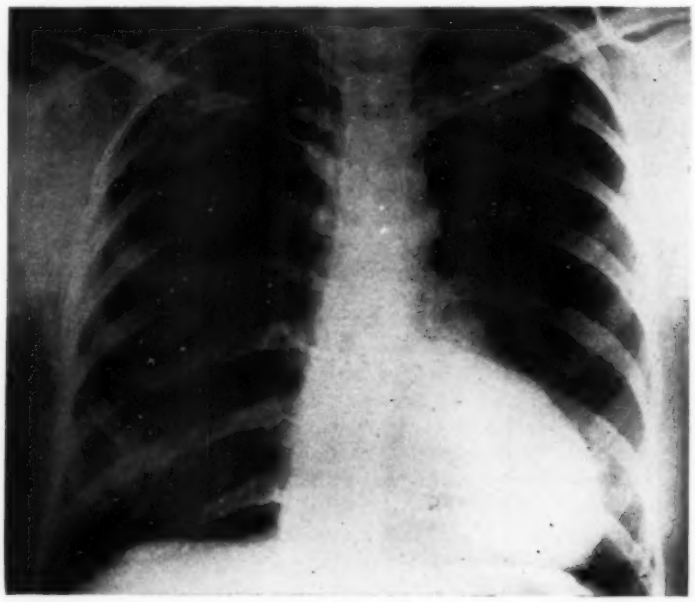

Fig. 1.—Anteroposterior roentgenogram of the chest. Note moderate enlargement of the heart and normal pulmonary and aortic silhouettes.

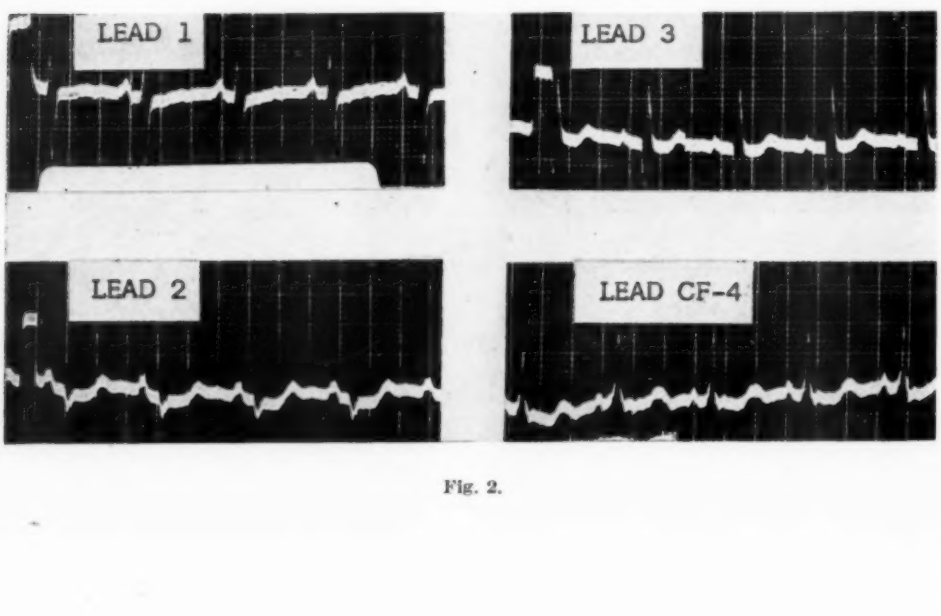

Fig. 2.

The urine contained 1 plus albumin, no sugar, and an occasional white and rare red blood cell. Five blood cultures were sterile.

From the day of admission, the patient ran a low grade fever which rose to 103.6°F. on the fifth hospital day. At this time she complained of pain in the right calf and of numbness in the toes of the right foot. The right foot was cooler than the left. No pulsations were obtained in the right dorsalis pedis and posterior tibial arteries. There was exquisite tenderness in the right calf. Pulsations were absent in the right upper extremity below the level of the brachial artery. The clinical impression was that the patient had developed multiple intravascular thrombi. Dicumarol and vasodilator drugs were administered, and a phlebotomy was done, removing 500 c.c. of blood. There was no improvement. Her course was progressively downhill, and she died on the twenty-fourth hospital day.

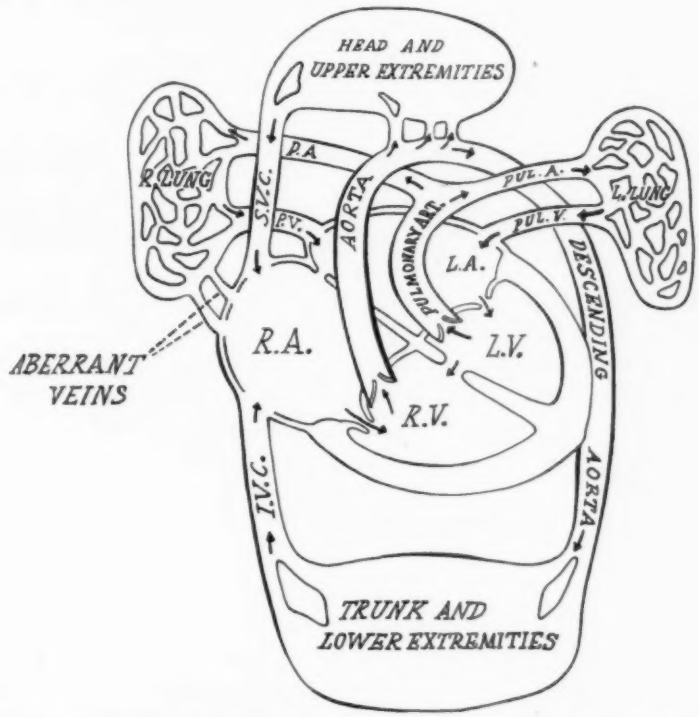

Fig. 3.—Complete transposition of the great vessels with ventricular septal defect and patent foramen ovale and two aberrant veins entering the right atrium.

Autopsy Report.—

Heart: The aorta enters the right ventricle. The pulmonary artery proceeds from the left ventricle to both lungs. The pulmonary veins enter the left atrium except for two aberrant veins which enter the right atrium from the right lower and middle lobes of the lung. Both ventricles are hypertrophied, but the heart is of approximately normal size. The weight was 400 grams. The valves show nothing of note on either side of the heart. The sinuses of Valsalva are patent and are in their usual positions in the aorta. Between the two ventricles there is a septal defect measuring 2 cm. in its greatest diameter. The defect is in the upper part of the septum immediately adjacent to the commisure of the aortic and pulmonary valves. In the atrium there is a patent foramen ovale. The coronary arteries are patent, soft, and show no evidence of sclerosis. The aorta is smooth and glistening. The right atrium receives the venae cavae. The latter show no structural abnormalities (Fig. 3).

COMMENT

In the differential diagnosis of congenital cardiac malformations resulting in permanent cyanosis encountered in adult life, three types of anomalies are usually considered: (1) the tetralogy of Fallot, (2) Eisenmenger's complex, and (3) pulmonary stenosis with auricular septal defect. Transposition of the great vessels is so rare in patients beyond the adolescent period that it is not considered in a diagnostic discussion of cyanosis in adults. Such indeed was our experience, and we were very much surprised to note the autopsy findings.

The basic pattern of the malformation consists of an aorta that arises from the right ventricle and a pulmonary artery that arises from the left ventricle. Taussig[1] has summarized the circulatory difficulties imposed by this anomaly. We found in the literature only one record of a patient with this type of malformation who survived past middle age. This was the patient 44½ years old at death reported by Carns, Ritchie, and Musser.[4] Our patient, who lived to the age of 38 years, presents therefore a rare phenomenon.

Aside, however, from the rarity of the malformation at this age, there are other features in our case that merit comment. Taussig[1] found characteristic roentgenographic and fluoroscopic changes in cases of transposition of the large vessels in infants. Marked enlargement of both ventricles, absence of the normal fullness of the pulmonary arc, and narrowing of the aortic silhouette constitute the diagnotic criteria. It is of interest that our case presented none of these features: the ventricles were only moderately enlarged, the fullness of the pulmonary arc was not absent, and the aorta appeared normal. The absence of marked cardiac enlargement indicates that the myocardium was able to bear the increased load imposed by the malformations and the associated cyanosis with little difficulty. This good cardiac reserve also helps to explain the length of life and the ability of our patient to carry a child to full term and to go through a puerperium without any untoward symptoms or signs. Lewis[5] has already stressed the extraordinary capacity of congenitally malformed hearts to cope with the increased load imposed by the malformations and has pointed out that "the immunity is due to the burden arising out of a congenital, and not out of an inflammatory or degenerative cause—the hypertrophied muscle is healthy and its strength is therefore unimpaired." This concept is of importance in the theoretical and practical consideration of the relation of effort to heart failure. Instances such as described in this communication indicate that it is the state of the myocardium rather than the extra burden of a valvular or congenital heart defect that determines the ability of the heart to carry on a normal circulation.

SUMMARY

A case of a woman with transposition of the large vessels, interventricular septal defect, and persistent foramen ovale, who lived to the age of 38 years, is presented. The absence of marked cardiac enlargement and the maintenance of an adequate cardiac reserve throughout life are interesting features of the case.

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Review of Recent Advances

BACTERIAL ENDOCARDITIS

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ALTHOUGH it has been nine years since the first patients with bacterial endocarditis were cured with penicillin[1] and seven years since the first report of a successfully treated series of patients,[2] there are still unsolved problems related to this disease. In particular, there is no unanimity of opinion as to the optimal therapy. New antibiotics have been appearing with gratifying rapidity, and many of them are active against the organisms commonly found in bacterial vegetations. Their place in management of this infection needs careful evaluation, especially in regard to endocarditis caused by penicillin-resistant organisms. Much new evidence bearing on the pathogenesis, the diagnosis, and the mechanisms involved in the cure of bacterial endocarditis has come out in recent years. The proper handling of patients with this disease requires a knowledge not only of classical cardiology, but of the interpretation of bacteriologic data as well, and an understanding of the complexities of the mechanisms involved in the relation between host, bacterial parasites, and antibacterial agents.

There is some evidence that more cases caused by penicillin-resistant organisms are appearing in recent years, and it seems that rule-of-thumb therapy with 1 or 2 million units of penicillin a day may prove less and less adequate as time passes.

It therefore seems appropriate to review some of the pertinent work of the past few years.

INCIDENCE

There are no satisfactory data on the incidence of bacterial endocarditis. Figures compiled from hospital admission rates can be misleading in that changes may reflect only a difference in the numbers treated in the home or small hospital rather than in the large medical center, and not a true change in the incidence of the disease. Nevertheless, the admission rate at the Massachusetts General Hospital was reported as 1.12 per thousand in the years 1944 to 1946, falling to 0.59 per thousand in 1947 to 1949.[3] This suggests that the disease is becoming less common, perhaps in part as a result of the widespread use of antibiotics prophylactically and also in the treatment of undiagnosed febrile illness. Some patients are probably being cured in the early stages of the disease without its

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ever being recognized. The majority of patients who now arrive in the hospital with bacterial endocarditis have already had some therapy, and in many cases where there is strong presumptive evidence for the diagnosis, no positive blood cultures are ever obtained. Hence, no definitive diagnosis may be made, and the patient will not appear in the statistics as a proved case.

A higher proportion of patients harboring penicillin-resistant organisms is encountered currently in large hospitals than was the case in the early years of penicillin therapy. This experience has been widely true of staphylococcal infections of all sorts as well as in endocarditis. In one series of eighteen patients with staphylococcal endocarditis recently reported,[4] 66 per cent of the organisms were resistant to 1 unit or more of penicillin. It would appear that selection of penicillin-resistant strains of staphylococci is certainly taking place in hospital populations and possibly also in the population at large as a result of the widespread and often indiscriminate use of penicillin.[5] In fact, we have come to the point where penicillin alone cannot be considered as adequate therapy for serious staphylococcal infections in the absence of specific information from the laboratory that the strain in question is sensitive to penicillin.[6]

Fortunately, penicillin-resistant strains of gonococci, pneumococci, and group A beta-hemolytic streptococci have not been encountered clinically, and it has not been possible to "train" these organisms to grow in high concentrations of penicillin in vitro.

The nonhemolytic streptococci fall in an intermediate group. Although highly resistant strains exist, the majority are sensitive to penicillin and are not easily modified toward penicillin resistance on exposure to this antibiotic. Levinson and associates[4] reported that 20 per cent of forty-six patients with streptococcal bacterial endocarditis treated in recent years at Los Angeles County Hospital were infected with organisms resistant to penicillin; this is a higher incidence of resistant infections than has been reported in earlier series.[7,8] Whether this increase is apparent or real is not clear, but the fact remains that in present-day hospital practice a significant and probably growing proportion of penicillin-resistant cases is being encountered.

PATHOGENESIS

Studies by two groups of investigators in the past two years have thrown new light on the pathogenesis of bacterial endocarditis and have demonstrated new methods of producing the lesions in experimental animals. Highman and Altland[9] reported that rats exposed to simulated high altitudes over extended periods of time developed cardiac hypertrophy and dilatation accompanied by irregular, nodular thickening of the heart valves, especially of the mitral valve, and by thrombotic endocardial lesions predominantly along the line of closure. Some of the rats spontaneously developed bacterial implants as well. In a subsequent study[10] rats similarly exposed to an altitude of 25,000 feet, but also injected repeatedly with nonhemolytic streptococci intravenously, developed bacterial endocarditis with a much greater frequency than did normal rats similarly injected but not exposed to high altitude. Lillehei and his group,[11]

working on arteriovenous fistulas in dogs, found that progressive and fatal bacterial endocarditis developed spontaneously in many of the animals, occurring with high frequency in those having the largest shunts, particularly in old dogs. Many of the animals had nonbacterial vegetations as well, and the mitral valve was again most frequently involved. These experiments indicate that in animals the chronically overloaded heart is susceptible to valvular damage, probably from mechanical stress, and that in time thrombotic vegetations are formed which may then easily be infected by bacteria circulating in the blood stream to produce the typical lesions of bacterial endocarditis. Therapeutic studies employing these experimental infections have not yet been reported, but they will be of considerable interest.

PROPHYLAXIS

Ideally it would be desirable to prevent patients with valvular heart disease from getting bacterial endocarditis by some form of prophylaxis which would completely and permanently eliminate the occurrence of bacteremia. Since transitory invasion of the blood stream by bacteria is a frequent and to some extent unpredictable event which may follow as innocuous an episode as chewing on hard candy or the development of a minor respiratory infection, ideal prophylaxis would have to be continuous and for life. Unhappily, no agents have yet been found which prevent bacteremia from occurring, although penicillin and aureomycin have been shown[12,13] to reduce its incidence following tooth extractions. Sulfadiazine is known to be inadequate.[13,14] There have as yet been no reports of the use of chloramphenicol or terramycin in this manner, but a priori it seems unlikely that they would be as effective as penicillin, first, because they are not bactericidal for the nonhemolytic streptococci and, second, because they have frequently failed to sterilize the blood stream in the treatment of bacterial endocarditis. In any event, should one or another of these agents prove effective in eliminating organisms from the blood, it would not be feasible to administer it continuously for years on end because of expense, side effects, and replacement of drug-sensitive bacteria by resistant ones.

The only practicable prophylaxis at the present time is aimed at preventing the development of bacterial implants in vulnerable patients who already have valvular damage and who are undergoing procedures known to be associated with bacteremia. These situations comprise operations in infected fields, such as dental extractions or procedures on the nasopharynx, colon, or genitourinary tract. Included in the latter group should be cystoscopy and normal delivery, both of which have been followed by bacterial endocarditis in a significant number of instances.

There are no data as yet which establish the value of any particular prophylactic regimen, and it will take years to accumulate enough information to settle this problem. Penicillin given in doses of 1 to 2 million units a day is usually recommended. While this may seem unnecessarily lavish, there have been several reports of the failure of smaller doses of penicillin to protect.[14-17] Administration of the drug for twelve hours before and at least forty-eight hours after operation is advised with the object of killing in situ any bacteria which get to the heart valves before a vegetation can be established.

There is urgent need for education of doctors and dentists, as well as patients with predisposing heart disease, concerning prophylaxis. Many patients with rheumatic hearts are still having teeth pulled without any antibiotic coverage, never having been warned by their doctor of the need for it.

DIAGNOSIS

Friedberg,[18] in reviewing the experience with bacterial endocarditis at Mount Sinai Hospital, came to the conclusion that many of the treatment failures could be directly attributed to a delay in making the proper diagnosis and starting treatment. He advocated making a diagnosis of bacterial endocarditis in any patient with valvular heart disease who runs fever for more than a week if no other cause can be found, even though the other clinical features of the disease are absent. There can be no doubt about the desirability of making the diagnosis early, nor about the importance of getting treatment under way at the earliest possible time. On the other hand, the premature administration of antibiotics to patients before serious efforts have been made to recover the infecting organism is unwise and may lead to the inadequate therapy of resistant infections. Somewhere one must strike a happy medium between delaying treatment until classical signs appear and starting prematurely. Embolic lesions, splenomegaly, anemia, microscopic hematuria, changing murmurs, and clubbing of the fingers may all be absent in the early stages. On the other hand, treating every patient who happens to have a heart murmur and also has fever from respiratory infection, rheumatic activity, Hodgkin's disease, or some other unrelated process is obviously undesirable. When a patient with valvular heart disease develops persistent fever or, for that matter, feels poorly in any obscure way even without showing prominent fever, bacterial endocarditis must be considered and appropriate diagnostic measures taken without delay. If the patient's clinical condition is not precarious and if the aortic valve is not involved, it is reasonable to withhold therapy for a few days until the clinical situation becomes clarified and until blood cultures can be evaluated at least in a preliminary way. Clinical judgment must be used in determining when or whether to institute therapy in a case where the diagnosis is unestablished and no positive blood cultures have been obtained. No hard and fast rules can be laid down to cover this situation, but it is safe to say that if there continues to be reasonable doubt that the patient might have bacterial endocarditis after a careful work-up and repeated observations over a reasonable period of time, therapy should be begun even though blood cultures remain negative. When, on the other hand, the clinical picture is highly suggestive, embolic phenomena, Osler's nodes, clubbing, or splenomegaly is present, or the patient's clinical condition is precarious by virtue of involvement of the aortic valve, the development of cardiac decompensation, or the presence of serious coexisting disease, treatment should be commenced without unnecessary delay. Five or six blood cultures can be obtained at hourly intervals before therapy is started, and the chances of recovering organisms are fairly good unless the patient has received antibiotics in the recent past. Once blood cultures are under way and treatment has been started, daily blood cultures should

be taken for several days in order to evaluate the adequacy of the therapeutic regimen. If the blood stream is not sterilized in two or three days, the treatment is probably inadequate.

It cannot be stressed too strongly that the diagnosis of bacterial endocarditis is incomplete unless the infecting agent has been recovered and its sensitivity to antibiotics determined.

While the nonhemolytic streptococci (that is, all streptococci other than the beta hemolytic) usually grow out in blood cultures after two or three days incubation, occasional strains are slower growing and do not appear in the culture flasks before two or three weeks. Culture methods must also be designed to reveal the presence of other organisms which are less frequently encountered in bacterial endocarditis. Hence, blood cultures should not only be kept for at least three weeks, but also some should be grown anaerobically, under CO_2, and at room temperature. The use of penicillinase is advisable if the patient has recently been on penicillin. Doses of penicillin far smaller than those used in the treatment of bacterial endocarditis may temporarily sterilize the blood stream and interfere with the recovery of organisms from blood cultures even with the addition of penicillinase.

ANTIBIOTIC SENSITIVITY TESTS

The laboratory tests commonly used to determine the "sensitivity" of an organism to an antibiotic measure the amount of antibiotic required to prevent *visible growth* of a certain inoculum, either in tubes or on agar plates. It is important to note that these tests measure only the bacteriostatic effects of drugs and tell us nothing about bactericidal activity, that is, whether the organisms are being killed. This may be of more than academic interest as we shall see later, for there is evidence to suggest that the therapeutic problem in bacterial endocarditis is to eradicate the infection by killing all of the organisms in the vegetation. No simple laboratory procedures have yet been developed which give quick and reliable information as to the bactericidal effects of antibiotics. Most of the work done in this field has involved the counting of viable organisms at various time intervals, thus establishing "growth" or "killing" curves which give precise information concerning the effect of the drugs on the bacterial population investigated. Such studies have shown that penicillin is actively bactericidal for growing populations of *most* organisms which are "sensitive" to it by inhibition tests.[19-22] The enterococci, however, and some strains of *Streptococcus viridans* are killed only very slowly and incompletely by penicillin alone. The addition of streptomycin, even though it may be completely inactive by itself, greatly enhances the bactericidal activity of penicillin against most of these resistant streptococci.[23,25] The newer antibiotics, aureomycin, chloramphenicol, and terramycin, are all primarily bacteriostatic for the nonhemolytic streptococci as well as for other organisms against which they are active. Under some circumstances[25,26] the combination of one of these agents with streptomycin may be bactericidal, but, oddly enough, the addition of any one of them to penicillin usually *decreases* the bactericidal effect of the latter.[25-28] The clinical importance

of these observations remains to be established, but the report by Jawetz and his group[29,30] that penicillin and chloramphenicol were less effective than penicillin alone in protecting mice against beta-hemolytic streptococcal infections suggests that this is not just another in vitro observation which may have no bearing on disease in the animal host.

The problems raised by the questions of synergisms and antagonisms between antibacterial drugs are by no means settled. Effects observed under one set of circumstances and for one group of organisms do not necessarily apply to others. Some combinations may be synergistic when bacteriostasis is the measure of activity, for example, penicillin and aureomycin,[6] and yet there is antagonism between the same two when bacterial killing is measured. With these facts in mind it is obvious that we must take our bacteriologic tests for what they are and realize that they give information only about the effects which they measure.

RELATIONS BETWEEN HOST, BACTERIA, AND ANTIBACTERIAL AGENTS

Many years of experience with bacterial endocarditis before the days of antibacterial chemotherapy established clearly the fact that host factors alone almost never cure the infection. It is true that the course of the untreated disease is often indolent and that the vegetations at autopsy frequently show areas of healing, but elsewhere bacteria almost always survive and eventually kill the host. Thus, mechanisms such as antibody formation, phagocytosis, scarring, and endothelial proliferation by themselves are unable to cope with this particular infection.

Next we may ask what happens if an agent is used which slows down the multiplication of the organisms but does not kill them, i.e., a bacteriostatic agent. In many infections this type of effect is sufficient to tip the balance in favor of the host, whose defenses are then able to cope with the static bacterial invaders and eventually eliminate them, as in lobar pneumonia, for example, or in acute hemolytic streptococcal cellulitis.

The evidence to date indicates that this is *not* the case in bacterial endocarditis. The sulfonamides are bacteriostatic for most strains of streptococci, yet only 5 to 10 per cent of the patients treated intensively with these drugs were cured. Typically, there was a temporary clinical improvement and perhaps sterilization of the blood stream during therapy, but relapse occurred within a short time with discouraging regularity. From the data available at present much the same sort of thing seems to be happening with the newer antibiotics aureomycin and Chloromycetin, both of which are again largely bacteriostatic. Kane and Finn,[31] in surveying the literature and reporting some cases of their own, found a total of five cures with aureomycin alone out of twenty-one cases treated. It is worthy of note that in these cases the organisms were highly sensitive to aureomycin by inhibition tests and yet the blood cultures remained positive all through treatment in many of them. The data on Chloromycetin and terramycin are too scanty to be of much value, but several failures have occurred with each of them, and a similar discrepancy between the "sensitivity" of the organism and the clinical outcome[31-34] has been observed.

Penicillin differs from the last-mentioned antibacterial agents in being actively bactericidal, at least for growing organisms. Perhaps its effectiveness in bacterial endocarditis is due to some other property, but the sum total of the evidence suggests rather strongly that, in the absence of host factors capable of eliminating all of the infecting bacteria, a therapeutic regimen should be designed to eradicate rather than merely to suppress the invaders.

Some of the difficulty in accomplishing successful eradication may be attributed to the relative inaccessibility of the bacteria which are buried in a mass of fibrin and necrotic valve substance and are not in close contact with the blood stream or with phagocytic cells. In this connection it has been shown[75,76] that sulfonamides do not penetrate fibrin readily whereas penicillin and streptomycin do. Satisfactory data concerning the activity of the new antibiotics in fibrin are not available, but preliminary experiments in the author's laboratory have shown that nonhemolytic streptococci grown in vitro in blood clots survive exposure to all the antibiotics tested longer than do the same organisms exposed in fluid media. This protective effect of clots is particularly striking against the combination of terramycin with streptomycin which is bactericidal in broth but only bacteriostatic in clots. Penicillin or penicillin and streptomycin, on the other hand, are usually bactericidal in clots, but somewhat more slowly so than in fluid media. The mechanisms which allow organisms to survive otherwise lethal antibiotic exposure in clots have not yet been worked out. Some possibilities are that the antibiotics do not diffuse into the fibrin or are inactivated by it, that organisms survive in leucocytes, or that they enter a resting phase which renders them refractory to the antibiotic action.

That some patients with bacterial endocarditis recover without having their vegetations sterilized by bactericidal agents is undoubtedly true, but the majority of the evidence indicates that healing of vegetations is a very slow process requiring months for completion,[37] and numerous cases have been reported where suppressive antibacterial therapy over many months failed, but the patient was cured eventually by an intensive course of treatment lasting but a few weeks.[38] There is still no complete agreement as to the optimum duration of therapy. Recommendations of various authors vary from two to eight weeks or longer.[39,40] On the basis of present information, it is the author's opinion that four weeks is long enough in the average case where the organism is sensitive to (and is probably actively killed by) penicillin in concentrations of 0.1 unit per milliliter. Experiments are being conducted at present to see whether shorter courses employing highly bactericidal combinations of drugs can be safely used.[25] Longer courses of six to eight weeks are probably indicated for infections caused by the enterococci and other resistant organisms which are known to be killed more slowly in vitro or by bacteria for which no bactericidal regimen can be found.

TREATMENT

The central principle of the antibiotic therapy of bacterial endocarditis should be the administration of a drug or combination of drugs which is the most rapidly and completely bactericidal for the infecting organism. In the average

case of penicillin-sensitive streptococcal bacterial endocarditis any of a number of penicillin dosage schedules has proved effective. The daily dose recommended has tended to creep up and up because of the occurrence of a few relapses after administration of smaller amounts. Thus, Christie,[41] reporting on large-scale clinical trials in England, abandoned schedules employing 500,000 units daily after 7 per cent and 14 per cent of the patients in two series relapsed. He now recommends giving 2 million units daily for one month, the first eighteen patients so treated having experienced no relapses or failures. Experimental regimens designed to shorten the time of treatment show promise, but cannot yet be recommended since the number of patients treated is small.

Enterococcus infections, which make up about 4 per cent of the cases of bacterial endocarditis seen in hospital practice, deserve special mention since they pose a difficult therapeutic problem. With penicillin alone, even in very high dosage, and the use of agents such as caronamide to raise penicillin blood levels still further, results have been disappointing.[42] The most favorable clinical results have been obtained with penicillin in large doses, 10 to 20 million units, plus streptomycin, 2 Gm. daily.[38,43-46] In vitro studies by Jawetz and his group and Hunter have shown that penicillin, even at optimal concentrations, kills this organism but slowly and incompletely. Streptomycin by itself is usually totally inactive, and yet, when it is combined with penicillin, a marked enhancement of the bactericidal effect is produced. Aureomycin and Chloromycetin, while they are active inhibitors of these organisms in low concentrations, are not bactericidal by themselves and, when combined with penicillin, slow down its killing effect. Clinical results again tend to parallel the in vitro findings of bactericidal activity so far as they go. Aureomycin, although it has been recommended for enterococcal endocarditis, has failed in six of eight cases reported in the literature.[31] Experience with the other newer antibiotics and with combinations of these with penicillin and streptomycin is too small to warrant drawing conclusions, except that results at the Mayo Clinic with terramycin and streptomycin combined have been unfavorable.[33]

It is important to recognize enterococcal infections early and to embark immediately on intensive combined treatment with penicillin and streptomycin even though the organism requires 10 or more units of penicillin for inhibition and is completely resistant to streptomycin. One must not be deluded by sensitivity tests into employing aureomycin or chloramphenicol as the drug of choice. Should penicillin and streptomycin fail, however, one of these drugs may be tried in combination with streptomycin or penicillin as a second choice. Eighth nerve damage is likely to result from the large amounts of streptomycin administered, but this is a relatively small price to pay in the cure of an otherwise lethal disease.

Endocarditis caused by gram-negative bacilli has also proved very refractory to treatment,[47,48] the failures far outnumbering the cures. There is insufficient clinical laboratory information about this type of infection to form a basis for dogmatic recommendations at present. By analogy, however, some suggestions can be offered. Streptomycin alone has frequently failed, and organisms rapidly become resistant to this agent when it is employed alone. It is reasonable to try

streptomycin in combination with aureomycin, chloramphenicol, or terramycin as a first choice, possibly thus achieving both a bactericidal effect and a delay in the emergence of streptomycin-resistant bacteria. One other reason for suggesting this type of combination is the report by Herrell[49] of the effectiveness of aureomycin and streptomycin in brucellosis.

Polymyxin B,[50,51,52] a polypeptide antibiotic which is actively bactericidal against many of the gram-negative bacilli, has had limited use, primarily because of its toxicity to the renal tubules. One is justified in accepting the risk of kidney damage in patients with endocarditis due to gram-negative organisms which are resistant to other antibiotics, especially in infections caused by *Pseudomonas aeruginosa* or *Bacillus proteus*.

PROGNOSIS

The average cure rate in bacterial endocarditis since the advent of penicillin has remained at approximately 70 per cent[17,53] although the figures in selected series[39,41] have been somewhat better. About 20 per cent of the patients die of causes other than uncontrolled infection, chiefly from heart failure, cerebral vascular accidents, and renal insufficiency. The prognosis in an individual case is influenced most critically by the degree of cardiac damage present. Those with severe valvular injury, particularly of the aortic valve, have the poorest outlook, and the appearance of congestive heart failure in the course of the disease is an ominous sign.[53]

Relapses occur most commonly within two weeks of the end of treatment and are uncommon after one month. After that period, it may be difficult to distinguish between relapse and reinfection. According to Christie,[41] the rate of reinfection approximates 2 per cent per year in patients cured of the disease.

It is difficult to tell whether or not a patient's vegetations have been permanently sterilized while therapy is in progress. Many of the clinical signs suggesting continued activity may persist for weeks or even months after cure. Low-grade fever, embolic phenomena, and elevation of the sedimentation rate quite commonly are found to outlast the active disease by several weeks. The finding of positive blood cultures after a few days of treatment, however, usually indicates that the therapy is inadequate and calls for a revision of the therapeutic regimen.

Finally, it should be emphasized that failure of one or two courses of treatment cannot be taken as evidence that success is impossible. As long as the patient's clinical condition has not deteriorated hopelessly, one must be prepared to try new and more heroic measures with the guidance of good laboratory help in searching for a regimen which will eradicate the infection. Eventual cures have been obtained after as many as five relapses.

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